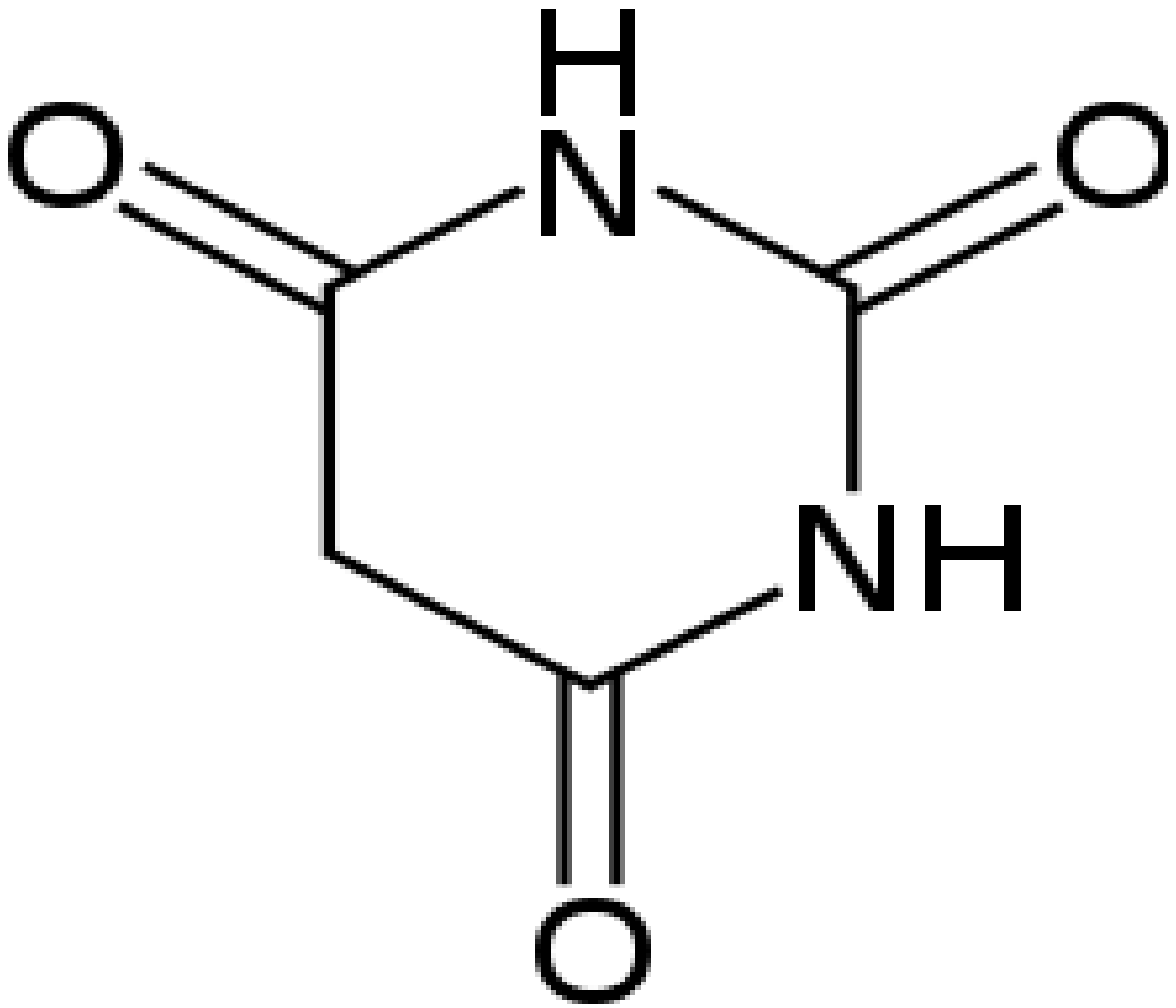
Sedative –hypnotic drugs

A sedative is defined as a compound that calm anxious and restless individuals .hyonotics cause drowsiness and facilitate sleep which is close to the normal pattern .

Barbiturates

MEDICINAL CHEMISTRY

Barbiturates are malonylurea derivatives (diureides), synthesized from malonic acid and urea .The electron negative carbonyl carbons confer an acidic nature to the molecule, thus classifying them as weak acids. Allyl, alkyl, and allocyclic side chains determine their pharmacological classification.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PHARMACOLOGY AND CLINICAL USE

Pharmacologically and clinically, barbiturates are classified according to their duration of effect. The presence of longer and bulkier aliphatic and allocyclic side chains produces compounds that range from short-, and intermediate to long-acting.

Their major action is the production of sedation, hypnosis, or anesthesia through central nervous system (CNS) depression.

The effect, however, depends largely on the dose, mental status of the patient or individual at the time of ingestion, duration of action of the drug, the physical environment while under the influence, and tolerance of the individual to this class of drugs.

These factors determine the probability of a therapeutic or euphoric response.

TOXICOKINETICS AND METABOLISM

- n general, an increase in the number of carbons and bulkier side chains results in enhanced lipid solubility, with a corresponding increase in toxicity. Attachment of a methylbutyl (1-mb) and replacement of the C2

with a sulfur group (as with thiopental) decreases its electron negativity, making it less acidic, more lipid soluble. Consequently, thiopental is an ultrashort-acting barbiturate used exclusively as a preoperative sedative/hypnotic.

- As a class, the barbiturates are largely nonionic, lipid-soluble compounds, and their pKa ranges between 7.2 and 7.9. The dissociation constants, therefore, do not account for differences in duration of action, especially with the long-acting compounds.

- Rapid movement into and out of the CNS appears to determine rapid onset and short duration. Conversely, the barbiturates with the slowest onset and longest duration of action contain the most polar side chains (ethyl and phenyl with phenobarbital structure,

- phenobarbital enters and leaves the CNS very slowly as compared to the more lipophilic thiopental (with intermediate pKa). In addition, the lipid barriers to drug metabolizing enzymes lead to a slower metabolism for the more polar barbiturates, considering that phenobarbital is metabolized to the extent of 10% per day. Similarly, distribution in biological compartments, especially the CNS, is governed by lipid solubility.

- Metabolism of oxybarbiturates occurs primarily in liver, whereas thiobarbiturates are also metabolized, to a limited extent, in kidney and brain. Phase I reactions introduce polar groups at the C5 position of oxybarbiturates, transforming the radicals to alcohols, ketones, and carboxylic acids. These inactive metabolites are eliminated in urine as glucuronide conjugates..

- Thiobarbiturates undergo desulfuration, to corresponding oxybarbiturates, and opening of the barbituric acid ring. Side chain oxidation at the C5 position is the most important biotransformation reaction leading to drug detoxification

MECHANISM OF TOXICITY

- CNS depression accounts for all of the toxic manifestations of barbiturate poisoning.
- The drugs bind to an allosteric site on the the GABA-Cl ionophore complex (-aminobutyric acid), an inhibitory neurotransmitter, in presynaptic or postsynaptic neuronal terminals in the CNS.
- This complex formation prolongs the opening of the chloride channel. Ultimately, by binding to GABA
- receptors, barbiturates diminish the action of facilitated neurons and enhance the action of inhibitory neurons.

Barbiturates concomitantly stimulate the release of GABA at sensitive synapses. Thus, the chemicals have GABA-like effects by decreasing the activity of facilitated neurons and enhancing inhibitory GABA-ergic neurons.

Two major consequences account for the toxic manifestations:

1. Barbiturates decrease postsynaptic depolarization by acetylcholine, with ensuing postsynaptic block, resulting in smooth, skeletal, and cardiac muscle depression.

2. At higher doses, barbiturates depress medullary respiratory centers, resulting in inhibition of all three respiratory drives.

The **neurogenic drive** , important in maintaining respiratory rhythm during sleep, is initially inhibited. Interference with carotid and aortic chemoreceptors and pH homeostasis disrupts the **chemical drive**. Lastly, interruption of carotid and aortic baroreceptors results in a decreased **hypoxic drive** for respiration. Thus, with increasing depth of depression of the CNS, the dominant respiratory drive shifts to the chemical and hypoxic drives.

SIGNS AND SYMPTOMS OF ACUTE TOXICITY

Signs and symptoms of barbiturate poisoning are related directly to CNS and cardiovascular depression. Reactions are dose-dependent and vary from mild sedation to complete paralysis.

Clinical signs and symptoms are more reliable indicators of clinical toxicity than plasma concentrations. This is especially true when CNS depression does not correlate with plasma concentrations, an indication that other CNS depressants may be involved.

SIGNS AND SYMPTOMS OF ACUTE TOXICITY

At the highest doses, blockade of sympathetic ganglia triggers hypotension, bradycardia, and decreased inotropy, with consequent decreased cardiac output. In addition, inhibition of medullary vasomotor centers induces arteriolar and venous dilation, further complicating the cerebral hypoxia and cardiac depression..

Respiratory acidosis results from accumulation of carbon dioxide, shifting pH balance to the formation of carbonic acid. rapid but shallow pulse, cold and sweaty skin (hypothermia), and either slow, or rapid, shallow breathing. Responsiveness and depth of coma are evaluated according to the guidelines for the four stages of coma

CLINICAL MANAGEMENT OF ACUTE OVERDOSE

Treatment of overdose is symptomatic and follows the general guidelines adapted from the Scandinavian method for symptomatic treatment for CNS depressants.

This includes maintaining adequate ventilation, keeping the patient warm, and supporting vital functions. To this end, oxygen support, forced diuresis, and administration of volume expanders has been shown to maintain blood pressure and adequate kidney perfusion and prevent circulatory collapse.

- If fewer than 24 h have elapsed since ingestion, gastric lavage, induction of apomorphine emesis, delivery of a saline cathartic or administration of activated charcoal, enhances elimination and decreases absorption, respectively. In particular, multidose activated charcoal (MDAC) increases the clearance and decreases the half-life of phenobarbital

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Alkalinization of the urine to a pH of 7.5 to 8.0 increases clearance of long-acting barbiturates, while short- and intermediate-acting compounds are not affected by changes in urine pH.

Should renal or cardiac failure, electrolyte abnormalities, or acid-base disturbances occur, hemodialysis is recommended.

Although most cases of phenobarbital overdose respond well to cardiopulmonary supportive care, severe cases will also require hemodialysis or charcoal hemoperfusion.

Neither of these procedures will remove significant amounts of short- or intermediate-acting barbiturates.

Through ion exchange, hemodialysis is more effective in removing long-acting barbiturates than short-acting compounds because there is less protein and lipid binding of the former. If renal and cardiac function are satisfactory, alkalinization of the urine and plasma with sodium bicarbonate promotes ionization of the acidic compounds.

BENZODIAZEPINES

The introduction of chlordiazepoxide in 1961 started the era of the benzodiazepines. Although this class of S/H did not render the barbiturates obsolete, the benzodiaz-epines have since enjoyed wide use as S/H, anxiolytics, anticonvulsants, preanesthetic sedatives and muscle relaxants. Their increased therapeutic index, relative to barbiturates, and lack of anesthetic properties have promoted the substitution of benzodiazepines for barbiturates.

PHARMACOLOGY AND MECHANISM OF TOXICITY

- Benzodiazepines bind to all three omega receptor subtypes in the areas of the limbic system, thalamus, and hypothalamus. Benzodiazepines bind to an allosteric site of the αand /orβ subunits of the GABA-Cl^- ionophore complex.
- This action increases the frequency of the opening of the chloride channels. Ultimately, the drugs enhance the affinity of GABA for GABA receptors and potentiate the effects of GABA throughout the nervous system. The effects of GABA-mediated actions account for benzodiazepines' sedative/hypnotic, anticonvulsant, and skeletal muscle relaxation properties.

At high doses, benzodiazepines induce neuromuscular blockade and cause vasodilation and hypotension . The compounds do not significantly alter ventilation, except in patients with respiratory complications, in the elderly population, and in the presence of alcohol or other S/H. There is also minimal effect on cardiovascular integrity

SIGNS AND SYMPTOMS OF ACUTE TOXICITY

Although signs and symptoms are generally nonspecific, apparent toxicity depends on the extent of intoxication. Serum toxic concentrations of benzodiazepines do not correlate well with signs and symptoms.

- Mild toxicity is characterized by ataxia, drowsiness, and motor incoordination. Psychologically, the patient displays different degrees of paranoia or erratic behavior and is easily aroused. In moderate toxicity, the patient is aroused by verbal stimulation, although he or she may enter coma stage one or two. Patients in severe toxicity are unresponsive except to deep pain stimulation, consistent with coma stage one or two.

Clinical management

Clinical management is symptomatic, and may also incorporate the use of a specifi c antidote. Flumazenil, a 1,4-imidazobenzodiazepine, is a benzodiazepine antagonist. It competitively antagonizes the binding and allosteric effects of benzodiazepines. Flumazenil completely reverses the sedative, anxiolytic, anticonvulsant, ataxic, anesthetic, comatose, and muscle relaxant effects.

Administration of 0.2 to 1.0 mg i.v. has an acute onset of 1 to 3 min and a peak effect at 6 to 10 min. Routine use of flumazenil, however, must allow for the determination of concomitant drug ingestion. The presence of stimulants such as cocaine, amphetamine, or tricyclic antidepressants precludes the routine use of the antidote, since the anticonvulsant effects of a benzodiazepine may be negated by flumazenil.

MISCELLANEOUS SEDATIVE/HYPNOTICS

- **C HLORAL H YDRATE**

Although it has no analgesic effect, and more effective, less toxic drugs are available, chloral hydrate is still used therapeutically as a S/H.

Currently available in oral liquid dosage forms only, the compound is lipid soluble, and is a derivative of chloral betaine and triclofos betaine and triclofos . The long-acting metabolite of chloral hydrate, trichloroethanol, is responsible for most of its toxicity, its low therapeutic index, and its undetectable presence in plasma.

Signs and symptoms of toxicity

- CNS depression, ataxia, gastrointestinal irritation, cardiovascular instability, and proteinuria. In addition, chloral hydrate significantly impairs myocardial contractility by sensitizing the myocardium to catecholamines . An increased risk of sudden death with chloral hydrate intoxication is a result of the development of arrhythmias. Beta-blockers, such as propranolol, are recommended in ameliorating chloral hydrate-induced cardiac arrhythmias.

MEPROBAMATE

A propanediol carbamate derivative, meprobamate is still marketed as an alternative S/H to barbiturates. It enjoyed some popularity until the introduction of benzodiazepines, yet its toxicity is similar to that of the barbiturates, including the production of ataxia and coma. Chronic use of the drug has been associated with severe hematopoietic disturbances such as aplastic anemia and thrombocytopenia.