❑ Lecture 3 in Clinical Toxicology

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Central Nervous System Depressants Toxicity

by

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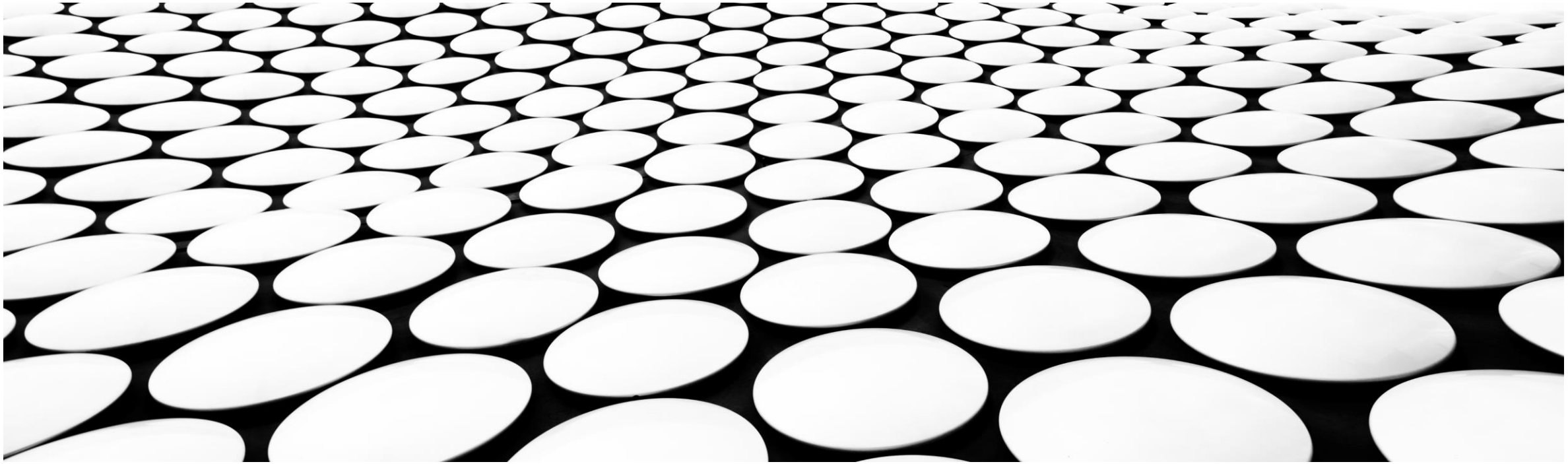

- Numerous drugs possess CNS-depressant activity.
- These include many sedative-hypnotic agents (Table 14.1).
- Dozens of other drugs that are used for various pharmacologic purposes produce sedation as an adverse effect!!!.
- Also, many chemicals cause drowsiness and CNS depression as a major component of toxicity. Thus, there are many categories of CNS depressants.

Table 14.1.Representative CNS* depressants

A-Barbiturates: Amobarbital, Butabarbital, Pentobarbital, Phenobarbital, and Secobarbital.

B-Non-barbiturate sedative/hypnotics: Bromides, Chloral hydrate ,Ethchlorvynol, Glutethimide, Meprobamate, Methaqualone, Methyprylon, and Paraldehyde

C-Benzodiazepines: Alprazolam, Chlorazepam, Chlordiazepoxide ,Chlorazepate, Diazepam, Flurazepam, Halazepam, Lorazepam ,Midazolam, Oxazepam, Prazepam, Temtizepam, and Triazolam

- A sedative is defined as a compound that calms anxious and restless individuals.
- Hypnotics cause drowsiness and facilitate sleep, which is close to the normal pattern.
- An anesthetic produces deep sleep, unlike natural sleep. A person who is asleep after a dose of a hypnotic-sedative can be aroused, but it is not possible with anesthesia-induced sleep.
- In a practical sense, the major difference among these three pharmacologic classes is the degree of CNS depression produced, which is related to dose.
- However, large doses of many anti-anxiety drugs can cause anesthesia, and smaller doses of a general anesthetic may produce mild sedation.

- **I- Barbiturates**: These drugs were divided into three groups based **on latency of onset and duration of action.**
- **Short-acting** barbiturates have a duration of action of 4 to 6 hrs., and include pentobarbital and secobarbital.
- **Intermediate-acting** barbiturates produce sedation persisting 8 to 10 hrs., and include amobarbital and butabarbital.
- **Long-acting barbiturates**, such as phenobarbital and barbital, have a duration of action of 12 to 24 hrs.
- Differences in potency!! of various barbiturates are minor.

- The short duration of action of certain barbiturates **cannot be equated with decreased toxicity potential**.
- In fact, just the opposite is true. Shorter acting barbiturates are more lipid soluble. Hence, they reach higher CNS concentrations and cause greater depression than phenobarbital.
- Furthermore, toxic blood concentrations of phenobarbital are more readily decreased by hemodialysis and alkaline diuresis than similar blood concentrations of short-acting barbiturates.

- Their potential for abuse was realized and misuse became widespread. At the same time, there was an increase in acute poisonings with barbiturates.
- Today, barbiturate poisonings are common in intentional (suicidal) poisonings, but less frequently encountered in accidental poisoning.
- Over 70% of suicides that occur annually are related to barbiturate overdose, either alone or with ethanol.
- One of the reported contributing factors to barbiturate poisoning is drug automatism. To illustrate, assume that an individual consumes a prescribed dose of sedative and becomes drowsy. Later, not remembering that he has already taken a previous dose(s), he swallows another dose. This act may be repeated again and again until a potentially lethal quantity has been consumed. An interesting speculation is that the term automatism may be used conveniently to explain why a victim of barbiturate or other central sedative intoxication died, rather than admitting it was a suicide.

- **Mechanism of Barbiturate Toxicity**: The most prominent toxic effect of barbiturate overdoses is classic, progressive CNS depression.
- Even when taken in large anesthetic doses, peripheral effects are minimal.
- If barbiturate-induced coma persists, toxic sequelae, including **cardiovascular, pulmonary, and other organ system complications may result.**

- Barbiturates depress the polysynaptic neuronal pathways primarily, with monosynaptic pathways affected to lesser extent. This action is believed to be due to a direct gamma-aminobutyricacid (GABA)-like effect, or to stimulation of GABA release.
- **GABA is an inhibitory neurotransmitter** within the CNS. When released, central depression is noted. The effect of barbiturates on GABA appears similar to that of benzodiazepines, except that not all barbiturate actions can be explained by this action.
- Other mechanisms include **an interaction with norepinephrine and acetylcholine.**
- Evidence for the significance of these actions in poisoning by barbiturates is not as convincing as for interaction with GABA.

- Sympathetic ganglia are depressed with larger doses. This may help explain why toxic barbiturate doses reduce the blood pressure.
- Normal doses do not cause significant cardiovascular effects, but only slight decreases in blood pressure and heart rate, as would be expected during sleep. High concentrations have direct myocardial suppressant actions, causing decreased force of contraction with reduced cardiac output.
- This, along with the effect on the sympathetic nervous system and developing anoxia from depressed respiration, helps explain the origin of shock that results from large doses.

- Other significant clinical features of barbiturate toxicity include decreased gastrointestinal motility and tone, which may lead to increased drug absorption.
- Bullous lesions on the fingers, buttocks, and around the knees have been reported in about 6% of all patients with acute barbiturate poisonings and may be helpful in differential diagnosis of an unconscious patient. These lesions are not seen exclusively with barbiturates, however.
- Recovery from barbiturate toxicity is usually complete after a prescribed treatment protocol. Complications, including hypostasis pneumonia, bronchopneumonia, lung abscesses pulmonary and cerebral edema, circulatory collapse, irreversible renal shutdown, and neurologic lesions, may result .Such complications are the usual cause of delayed death.

❑ Characteristics of Barbiturate Poisoning

- ❖ Barbiturates can produce a wide range of CNS effects varying from sedation to hypnosis, to anesthesia, and eventually to complete paralysis of central voluntary and involuntary functions.
- ❖ Extent of paralysis is dependent primarily on dose. Consequently, severity of CNS depression after barbiturate overdose is also a function of dose.
- ❖ Barbiturate poisoning can be expected to occur when 5 to 10 times the normal hypnotic dose is ingested.
- ❖ The normal hypnotic and, therefore, toxic doses for the classes of barbiturates varies because of differences in duration of action and lipid solubility.

- For example, Short-acting barbiturates are highly lipid soluble and potentially more toxic than long acting barbiturates, which are less lipid soluble. Lethal doses of short-acting barbiturates produce death in a short period of time. In suicides, victims are often found dead at the scene or they die shortly thereafter.
- In contrast, patients who overdose on long-acting barbiturates generally die later in the hospital. Caution should be exercised when attempting to relate reported blood concentration data to degree of poisoning. It must be remembered that these are not absolute values. They represent a range of blood concentrations indicating therapeutic, toxic, or lethal levels.
- Severity of barbiturate intoxication is better determined by the victim's clinical manifestations. Barbiturate blood concentrations are usually used to confirm the initial diagnosis. If the clinical features indicate signs of severe CNS depression, but laboratory results still show low blood barbiturate concentrations, this may indicate that one or more additional CNS-depressant drugs are involved. The most likely offender is ethanol.

- **II- Benzodiazepines**: Because of inherent dangers common to therapeutic and toxic doses of barbiturates and older non-barbiturate sedative-hypnotic compounds, drugs that are as pharmacologically effective as barbiturates, but possess a wider margin of safety, are constantly being developed. One of the outcomes of research is a class of drugs known as benzodiazepines. They represent the single most widely used group of sedative drugs.
- Benzodiazepines have a high therapeutic index and are the safest of all sedative-hypnotic drugs!!. In other words, the range between therapeutic dose and toxic or lethal dose is extremely wide. Increasing dosage, even to massive amounts, will not cause general anesthesia, as opposed to other sedative drugs. Consequently, their overall potential for toxicity is low, and patients with benzodiazepine overdose present with fewer problems.

TABLE 14.4. *Properties of representative benzodiazepine derivatives*

Drug	Oral dosage range	Peak oral plasma concentrations (hr)	Half-life (hr)	Major active metabolites (half-life in hr)	Elimination rate
Anxiolytics					
Diazepam (Valium)	6–40 mg/day	1–2	20–50	desmethyldiazepam (30–60)	slow
Chlordiazepoxide (Librium, Libritabs, various other)	15–100 mg/day	2–4	5–30	desmethylchlordiazepoxide, demoxepam, desmethyldiazepam	slow
Chlorazepate (Tranxene)	15–60 mg/day	—	30–60	desmethyldiazepam	slow
Prazepam (Centrax)	20–60 mg/day	6	78	3-hydroxyprazepam, desmethyldiazepam	slow
Halazepam (Paxipam)	60–160 mg/day	1–3	7	*n*-3-hydroxyhalazepam, desmethyldiazepam	slow
Oxazepam (Serax)	30–120 mg/day	1–2	5–10	None	rapid to intermediate
Lorazepam (Ativan)	2–6 mg/day	2	10–20	None	intermediate
Alprazolam (Xanax)	0.75–4 mg/day	0.7–1.6	12–19	α-hydroxyalprazolam	intermediate
Hypnotics					
Flurazepam (Dalmane)	15–60 mg	—	50–100	desalkylflurazepam (50–100)	slow
Temazepam (Restoril)	15–30 mg	2–3	9–12	None	intermediate
Triazolam (Halcion)	0.125–0.5 mg	0.5–1.5	2.3	α-hydroxytriazolam	rapid

❑ Mechanism of Benzodiazepine Toxicity

- ❑ Most toxic effects of benzodiazepines result from their sedative action on the CNS.
- ❑ At extremely high doses, neuromuscular blockade may occur. Also, after intravenous injection, peripheral vasodilation causes a fall in blood pressure, and shock may result. Within the CNS, benzodiazepines are selective for polysynaptic pathways.
- ❑ They inhibit presynaptic transmission by stimulating the inhibitory neurotransmitter, GABA. This action is believed to occur because the drugs antagonize a specific protein that normally inhibits binding of GABA to its receptor site. This effect is also generalized, occurring throughout the CNS.
- ❑ Although there is experimental evidence to suggest that benzodiazepines also stimulate or inhibit other central neurotransmitters, there are more supportive arguments for its effect on GABA.

- Respiration is not markedly affected, even with hypnotic doses of most benzodiazepines. Some derivatives may decrease alveolar ventilation (decreased P02, increased Pco2) and induce CO2 narcosis in persons with preexisting compromised respiratory functions (e.g., chronic obstructive pulmonary disease).
- Benzodiazepines potentiate the respiratory depressant effect produced by other sedative drugs when taken concomitantly. Most deaths associated with benzodiazepine overdose after oral ingestion have actually occurred in persons who ingested ethanol or another CNS depressant concurrently.
- Intravenous dosing has greater associated risk of life threatening hypotension and respiratory depression leading to death.

❑Characteristics of Benzodiazepine Poisoning

- ❖ Signs and symptoms of benzodiazepine overdose are presented in Table 14.5.
- ❖ Effects on motor performance are more prominent than cognition. On occasion, severe paranoia, psychosis, hallucinations, and hypomanic behavior are noted .
- ❖ Even in large doses, benzodiazepines cause little more than Stage **0 or Stage 1 coma** . The patient can still be aroused. When not arousable, or when cardiovascular and respiratory functions are severely depressed, other depressants may have been ingested .
- ❖ Serum benzodiazepine concentrations do not correlate well with toxic signs and symptoms. For diazepam, toxic blood concentrations are between 0.5 and 2.0 mg/dL.
- ❖ Tolerance to benzodiazepines can occur after chronic ingestion. There may be cross tolerance to barbiturates, methaqualone, and ethanol, also.

TABLE 14.5. *Characteristics of benzodiazepine toxicity*

Mild	Moderate	Severe
Ataxia	Responds to verbal stimuli	Responds only to deep pain
Drowsiness	Coma stage 0–1	Respiratory depression (rare)
		Hypotension (rare)
		Coma stage 1–2

Coma 1 (stage 1)	Responsive to painful stimuli but not to verbal or tactile stimuli; no disturbance in respiration or blood pressure
Coma 2 (stage 2)	Unconscious, not responsive to painful stimuli; no disturbance in respiration or blood pressure

❑ III- Other Depressants

- ❑ A- Chloral Hydrate Chloral hydrate, as well as chloral betaine and triclofos sodium, are potent CNS sedatives.
- ❖ Chloral hydrate is converted to its active metabolite, trichloroethanol. Chloral betaine and triclofos are converted to chloral hydrate and trichloroethanol, respectively.
- ❖ Chloral hydrate and metabolites of chloral betaine and triclofos are lipid soluble and readily enter the CNS.
- ❖ Poisoning resembles barbiturate intoxication. The LD50 for chloral hydrate in rats is 200 to 500 mg/kg. Significant toxicity occurs with doses >2 g. Lethal doses are between 5 and 10 g. Chloral hydrate and ethanol in combination are referred to as the infamous Mickey Finn.
- ❖ Whether intense CNS depression that results is additive or synergistic to the depressants is not known, it has been suggested that each drug inhibits the metabolism of the other . If this is true, the overall effect may be more than additive.
- ❖ The corrosive action of chloral hydrate may cause gastritis, nausea, and vomiting. In addition, it has been shown to be nephrotoxic and hepatotoxic.

❑B-Meprobamate:

- With introduction into medicine in the 1950s, meprobamate was an alternative to barbiturates for reducing anxiety. For nearly last decades, until the advent of benzodiazepines, meprobamate and its derivatives were the most commonly used non-barbiturate antianxiety drugs.
- Symptoms of meprobamate overdose are similar to those of barbiturates. Coma has been associated with blood concentrations between 10 and 20 mg/dL.
- The dosage range for severe toxicity is varied and probably due to individual differences in the rate of metabolism.
- Death results from irreversible shock, respiratory depression, and pulmonary edema. Twelve grams was fatal in one instance, whereas other patients have survived doses as high as 40 g .

❑ C- Antihistamines

- ❖ introduction of antihistamines in the late 1940s, it was realized quickly that these drugs produced a variety of effects centered around CNS depression.
- ❖ Sedation is the most common side effect of most antihistamines in adults (Table 14.6). In overdose, CNS depression leading to coma may result. However, additional symptoms that resemble anticholinergic actions may also be present, and may be more significant than the degree of depression.
- ❖ These include mydriasis, flushing, fever, dry mouth, and blurred vision.
- ❖ Children usually experience central stimulation, hallucinations, tonic-clonic convulsions, and hyperpyrexia, rather than depression.

TABLE 14.6. *Characteristics of antihistamine toxicity*

CNS effects		Anticholinergic effects
Children	Adults	
Excitement	Disorientation	Dilated pupils
Tremors	Ataxia	Blurred vision
Hyperactivity	Dizziness	Tachycardia
Hallucinations	Sedation	Warm skin
Hyperreflexia	Coma	Dry mouth
Convulsions		Diminished bowel sounds
		Urinary retention

❑Management Of CNS Depressant Drugs

- ❖Overdose Management of any CNS-depressant drug overdose follows the same basic principles. Most clinical experience has accumulated with management of barbiturate intoxications Therefore, management of barbiturate poisoning will serve as a model for the other CNS .
- ❖Survival after CNS depressant overdose is very good. Fewer than 2% of victims succumb (die). In the 1930s and 1940s, the primary treatment was directed toward decontamination by gastric lavage followed by very high doses of activated charcoal. This practice was replaced in the late 1940s and early 1950s with a protocol that called for administration of large doses of CNS stimulants (analeptics: e.g. methylphenidate).
- ❖Morbidity and mortality rates with this treatment often ran into the 40% to 50% range. Analeptic drugs stimulated respiration sufficiently, but also increased the brain's demand for oxygen. Added to this was an increased chance for convulsions and cardiac arrhythmias.
- ❖Today, analeptics are not part of the conventional treatment protocol.

- Vasopressors were formerly given to elevate blood pressure. They are no longer recommended. Rather, cautious fluid replacement and inotropic agents, such as dopamine and dobutamine, are preferred.
- Dopamine: is unique adrenomimetic drug in that it exerts cardiovascular actions by:
  - 1- Releasing epinephrine and nor-epinephrine from adrenergic neurons.
  - 2- Interacting with α and β1 receptors.
  - 3- Interacting with specific dopamine receptors. It has concentration dependent actions.
- Low doses of dopamine causes vasodilation in the renal, mesenteric, coronary, and cerebral vasculature. Such vasodilation cannot be antagonized by β-adrenergic blocker propranolol , but by dopaminergic receptor blockers like haloperidol or other acting to block dopamine receptors.

- Dopamine can exert pronounced cardiovascular and renal effects through the activation of both D1- and D2-receptor subtypes. Stimulation of the D1-receptor, which is present on blood vessels and certain other peripheral sites, will result in vasodilation, natriuresis, and diuresis. D2- receptors are found on ganglia, on sympathetic nerve terminals, on the adrenal cortex, and within the cardiovascular centers of the CNS; their activation produces hypotension, bradycardia, and regional vasodilation (e.g., renal vasodilation).The kidney appears to be a particularly rich source for endogenous dopamine in the periphery.

- The infusion of moderately higher concentrations of dopamine increases the rate and contractile force of the heart and augments the cardiac output. This action is mediated by β1-adrenoceptors and norepinephrine release and is antagonized by propranolol. Dopamine has a greater effect on the force than on cardiac rate.
- The advantage of this greater inotropic than chronotropic effect of dopamine is that it produces a smaller increase in oxygen demand by the heart .Systolic blood pressure is increased by dopamine, whereas diastolic pressure is usually not changed significantly.
- Total peripheral resistance is decreased because of the vasodilator effect of dopamine

- At still higher concentrations, dopamine causes α-adrenoceptor-mediated vasoconstriction in most vascular beds and stimulates the heart. Total peripheral resistance may be increased. If the concentration of dopamine reaching the tissue is high enough, vasoconstriction of the renal and mesenteric beds also occurs. The vasoconstrictive action of dopamine is antagonized by α-adrenoceptor blocking agents such as phentolamine.
- In the 1960s the Scandinavian Method for treating barbiturate intoxication was developed because it was recognized that the two most significant pathophysiologic effects of CNS-depressant toxicity were hypoxia and shock. The protocol (Fig. 14.1) originated with Scandinavian physicians. It stressed support of physiologic functions, good nursing care, and no analeptic or vasopressor therapy. Basic elements of the approach are still retained.

FIG. 14.1. Management of acute barbiturate poisoning.

- The highest priority in treating any victim of depressant poisoning is to stabilize respiration and correct anoxia. If the brain suffers damage from insufficient oxygenation, other procedures will be of little benefit. Oxygen should be given and the patient ventilated mechanically if needed.
- A cuffed endotracheal tube should be used in deep coma to decrease risk of aspiration pneumonia during lavage. To help prevent hypostatic pneumonia, the victim should be turned frequently.
- Prophylactic antibiotic treatment was thought to be beneficial. Now, it is considered unnecessary and can lead to superinfection.

- Since circulatory collapse is a major threat after ingestion of massive doses of CNS depressants, cardiovascular function must be assessed quickly and deficiencies corrected.
- The treatment of choice in circulatory shock is volume expansion with a fluid challenge followed by appropriate pressor agents (e.g., dopamine). Renal failure is the cause of one-sixth of all deaths .
- Therefore, kidney function must be monitored constantly. Signs of uremia may be an indication for hemoperfusion or hemodialysis.
- Once supportive measures have been established, blood and urine samples should be obtained for toxicologic analysis. Results of analysis can aid diagnosis and evaluation of effectiveness of treatment.

❑ Prevent Further Absorption of the Poison

- ❑ If no contraindication exists, ipecac-induced emesis should be considered. In a comatose individual, gastric lavage is appropriate.
- ❑ Activated charcoal adsorbs barbiturates and most other common CNS-depressant drugs. A slurry can be instilled into the stomach through a nasogastric tube. Studies have shown repeated activated charcoal treatment significantly decreases their plasma half-life .
- ❑ In some cases, this procedure works as well as hemodialysis and hemoperfusion . A cathartic should be given to enhance elimination of the remaining drug.

- Increase Excretion of Absorbed Drug Increased excretion of the absorbed drug may be accomplished by repeated doses of activated charcoal, diuresis, dialysis, or hemoperfusion.
- Barbiturates are weak acids, varying from pKa 7.2 for phenobarbital, to 8.1 for secobarbital. Thus, alkalinization will promote ionization of at least half the drug in the glomerular filtrate and cause it to be excreted more readily.
- Only long-acting barbiturates, which are eliminated primarily via the kidney, are readily eliminated by alkalinization.
- Urinary alkalinization is ineffective for short- and intermediate-acting barbiturates, or for any of the other CNS depressants.

- Scientists have shown that multiple doses of activated charcoal starting 10 hrs. after phenobarbital ingestion in healthy individuals significantly reduce blood concentrations.
- Whereas controls had a phenobarbital half life of 110 hrs., activated charcoal reduced this to 20 hr. Since phenobarbital undergoes enterohepatic circulation, it is possible that activated charcoal may interfere with barbiturate reabsorption.
- Peritoneal dialysis increases elimination of some CNS depressants, but this procedure appears to be of low efficiency and is no longer recommended.
- Hemodialysis is variably effective in removing significant amounts of CNS depressants from blood in cases of toxic/lethal ingestions, or when the patient is in severe hemodynamic or renal compromise, and prolonged coma is likely. Hemoperfusion has been shown to effectively remove significant amounts of any of the CNS depressants discussed.

Benzodiazepine Antidote: Flumazenil (Mazicon), 1,4-imidazobenzodiazepine , is an antagonist that can reduce or terminate the sedative, anxiolytic, anticonvulsant, ataxic, anesthetic, and muscle relaxant effects of benzodiazepines in a dose dependent manner .Despite its short half-life, small doses (0.2 to 1.0 mg) of flumazenil are usually effective in reversing the sedative action of benzodiazepine poisonings. Flumazenil is generally well tolerated. Adverse effects are usually mild, consisting mainly of nausea and vomiting. The appearance of a withdrawal syndrome is possible due to displacement of the agonist from the receptor site, but the incidence is low.

Thanks for Listening

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