Sedative/Hypnotics

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NTRODUCTION

- Sedative-hypnotic drugs are used therapeutically to produce facilitate sleep.
- A variety of these agents have been developed over the past century, each with adverse effects, toxicity, and problems with tolerance as well as drug withdrawal.
- Chloral hydrate and the bromides, popular sedatives before 1900, were replaced by the barbiturates at the turn of the twentieth century. Recognition of the abuse potential of barbiturates led to the development of newer pharmacologic agents .

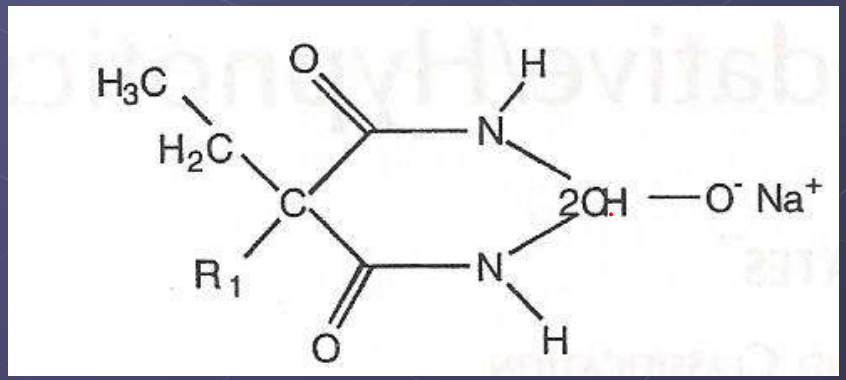
Most of these drugs, which include chloral hudrate and meprobamate., either have been withdrawn from the market are prescribed very infrequently toxicity and abuse potential.

The benzodiazepines were marketed as safe and non addictive sedative and anxiolytic agents but now are recognized as having significant potential for dependence.

- Today, the most popular therapeutic agents for anxiety(used for sedation),
- hypnosis (used for sleep), or
- a naesthesia for deep sleep include **Buspirone and Zolpiden**.
- Benzodiazepines are still frequently employed.
- Barbiturates are still the cause of 50,000 accidental and intentional poisonings per year, and their synergistic effects with ethanol are one of the leading causes of hospital admissions.

Barbiturates

- **Medicinal Chemistry** are malonylurea derivatives ,synthesized from malonic acid and urea .
- The electron negative carbonyl give an acidic nature to the molecule, this classifying them as weak acids.



Pharmacology and Clinical Use

- Barbiturates are traditionally classified as long, intermediate, short, and ultra-short acting based on the duration of action of a single dose in rabbits .
- The major action is the production of sedation. Hypnosis, or anesthesia **through CNS depression .**
- for instance, a 100 mg dose of secobarbital ingested in the home at bedtime to induce sleep would, most likely,only cause a mild euphoria in habitual user without significant sedation.

The effect depends largely on

- dose,
- mental status of patient
- duration of action of the drug,
- tolerance of the individual to this class of drugs.
- These factors determine the therapeutic or euphoric response.

Toxicokinetics and Metabolism

An increase in the number of carbons side chains results in enhanced lipid solubility, with corresponding increase in toxicity.

Replacement of the **C2** with sulfur group as with (**thiopental**)decreases its electron negativity, making it less acidic, more lipid soluble.

R1-ethyl and phenyl- most polar side chaine, slowest onset and longest duration.

Thus *phenobarbital enters the CNS very slow* as compared to the more **lipophilic thiopental**.

Properties of barbiturates

Properties of Barbiturates

Compounds[a]	R_1	Classification	Sedative/Hypnotic Dose (Total mg Daily)	Toxic Concentration (mg/dl)	$t_{1/2}$ (h)	pKa
Barbital	ethyl	LA	100–200/300–500	6–8	—	7.8
Phenobarbital	phenyl	LA	30–90/100–200	4–6	24–140	7.2
Amobarbital	isopentyl	IA	30–150/100–200	1–3	8–42	7.8
Pentobarbital	1-mb	SA	20–150/100	0.5–1.0	16–48	7.9
Secobarbital[b]	1-mb	SA	30–200/100	0.5–1.0	20–34	7.9
Thiopental	1-mb, C_2=S	UA	3–5 mg/kg	<0.5	<1	7.4

Note: R_1 = side group substitutions corresponding to Figure 11.1; 1-mb = 1-methylbutyl; LA = long-acting, IA = intermediate-acting, SA = short-acting, UA = ultrashort-acting.

[a] Grouped according to classification.

[b] The ethyl group for secobarbital is replaced by an allyl side chain.

Mechanism of Toxicity

- CNS depression accounts for all of barbiturate poisoning.
- The drugs bind to an allosteric site on the GABA-Cl, an inhibitory neurotransmitter, in presynaptic or postsynaptic neuronal terminals in the CNS.
- Positive modulation of the action of (GABAa) at receptors –anoxiolytic .-sedative, hypnotiecs,-general ansthetics.- anti covulsants.

- At higher doses, barbiturates depress medullary respiratory centers. resulting in inhibition of respiratory function.
- Barbiturates decrease postsynaptic depolarization by acetylcholine , due to postsynaptic block, resulting in smooth, skeletal, and cardiac muscle depression.

Signs and symptoms of Acute Toxicity

- Clinical sings and symptoms are more reliable indicators of clinical toxicity than plasma concentration.
- CNS depression of Barbiturates, does not correlate with plasma **concentration .**
- CNS effects include anticonvulsant, anesthetic, anxiolytic, and sedative-hypnotic actions.
- In particular, the hypoxic drive for respiration is sensitive to barbiturates.
- **Doses only three times greater than the usual hypnotic dose have been shown to depress respiratory drive**.

At the highest doses -hypotension , bradycardia, and decreased cardiac output.

Respiratory acidosis results from accumulation of carbon dioxide , shifting pH balance to the formation of carbonic acid.

The condition resembles alcoholic inebriation as the patient presents with hypoxic shock, rapid pulse, cold and sweaty skin, and slow or rapid, breathing.

- Delayed complications of acute renal failure, pneumonia, pulmonary edema, and cerebral edema.

- Hypotension, depth of coma, and excess fluid administration as risk factors.

Clinical management of acute overdoses

- Scandinavian method for symptomatic treatment for CNS depressants.

This includes maintaining the ventilation ,keeping the patient warm , supporting vital functions .

Oxygen support, forced diuresis , maintain blood pressure and kidney function.

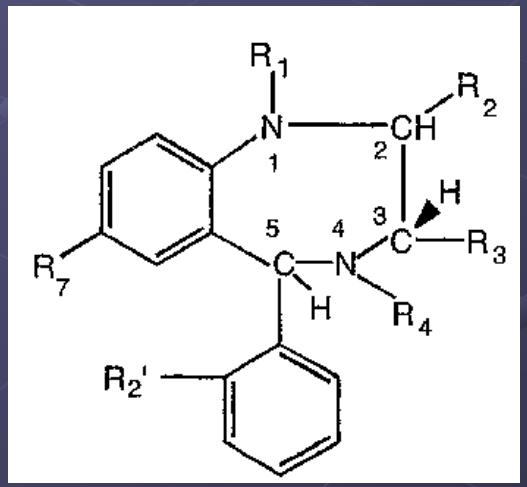
Multiple doses of activated charcoal (MDAC) have been shown to enhance the non renal clearance of intravenous phenobarbital .

Alkalinization of urine to a pH greater than 7.5 to 8.0 has been shown to enhance elimination of phenobarbital independent of urine flow rate.

Withdrawal syndromes of barbiturates. hallucinations, sleeplessness , vertigo, and convulsions ,depending upon the degree of dependency.

Benzodiazepines

- The Benzodiazepines wide use as S/H, anxiolytic, 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.



Medicinal chemistry

All the important benzodiazepine contain a 5-aryl-1,4-benzodiazepine structure.

The chemical nature of substituent's at positions 1 and 3 varies widely.

Their half- life correlates well with their duration of action ,as ell as duration of toxic manifestations.

Structure-activity relationship, however, has failed to correlate the pharmacological and toxicological profiles with the chemical structure.

Pharmacology and Mechanism of Toxicity

Benzodiazepine bind to all three omega receptor.

Benzodiazepine bind to a allosteric site of the (α,β́)GABA Cl- ionophore complex.

This action increases the frequency of the opening of the chloride channels.

At last, the drugs enhance the affinity of GABA for receptors.

- The effects of GABA- mediated action account for benzodiazepines S/H, anticonvulsant, and skeletal muscle relaxation properties.
- At high doses, benzodiazepines induce cause vasodilation and hypotension .

- The compound do not much change ventilation,

except the elderly population, and the presence of alcohol or other S/H.

- There is also minimal effect on cardiovascular .

Properties of benzodiazepines

Properties of Benzodiazepines

Generic Name[a]	Proprietary Name	Classification	Sedative/Hypnotic Total Daily Dosage (mg)	Toxic Concentration	$t_{1/2}$ (h)
Alprazolam	Xanax	Anxiolytic	0.25–1.5/0.5–1.0	0.4 µg/dl	12–19
Chlordiazepoxide	Librium	Anxiolytic	5–100/25–50	3.5–10 mg/l	7–28
Clorazepate	Tranxene	Anxiolytic-S/H	3.75–22.5/7.5–15	—	30–60
Diazepam	Valium	Anxiolytic-S/H, SKR, anticonvulsant	2–40/5–10	0.5–2.0 mg/dl	20–90
Flurazepam	Dalmane	Hypnotic	—/15–30	0.25 mg/dl	24–100
Lorazepam	Ativan	Anxiolytic-S/H, anticonvulsant	0.5–3.0/2–4	0.3 µg/dl	10–20
Oxazepam	Serax	Anxiolytic-S/H	10–120/10–30	3–5 mg/l	5–10
Temazepam	Restoril	S/H	—/7.5–30	1.0 mg/l	9–12
Triazolam	Halcion	Anxiolytic-S/H	0.25–1.5/0.125–0.5	7 µg/kg (toxic dose)	2–3

Note: S/H = sedative/hypnotic; SKR = skeletal muscle relaxant.

[a] Grouped by generic name.

Toxicokinetics

- All of benzodiazepines are completely absorbed, primarily due to their high nonionic/ionic ratio.
- Lipophilicity, polarity and electron negativity *different* by the various substituent's.

Signs and Symptoms of Acute Toxicity

In generally nonspecific, apparent toxicity depends on the extent of intoxication.

Serum toxic concentration of benzodiazepines do not correlate well with signs and symptoms.

Mild toxicity is characterized by ataxia, drowsiness, and motor in coordination.

In moderate toxicity, the patient is aroused by verbal stimulation, although may enter coma stage one or two.

In severe toxicity are unresponsive except to deep pain stimulation ,consistent with coma .

In general ,respiratory depression and hypotension **are rare**

Clinical Management of Acute Overdose

Clinical management is symptomatic, and also specific antidote**. Flumazenil,** a 1,4-imidazobenzodiazepine, is a benzodiazepine antagonist.

Flumazenil completely reverses the sedative, anticonvulsant, ataxic, anesthetic, comatose, and muscle relaxant effects.

Administration of 0,2to 1,0 mg i.v.

Has an acute start of 1 to 3 min and a peak effect at 6 to 10 min.

Tolerance and withdrawal.

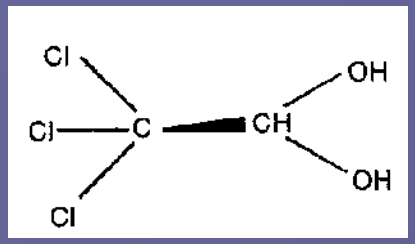
The withdrawal syndrome depending on the dose.

As with barbiturate and alcohol, benzodiazepine withdrawal sings and symptoms are similar.

hallucinations, sleeplessness , vertigo, and convulsions ,depending upon the degree of dependency.

Misellaneous sedative/hypnotics

- Chloral hydrate
- Mepromate
- Zolpidem tartrate
- Buspirone
- Flunitazepam
- GHB (Gamma-Hydroxybutyrate).



Chloral Hydrate

Althuogh it has no analgesic effect, and more effective, less toxic drug are available, as S/H.

Available in Oral liquid dosage forms only, the compound is lipid soluble.

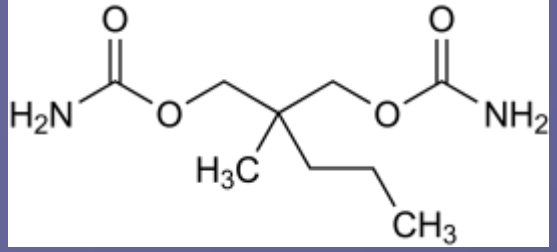
The long acting metabolite of chloral hydrate, Trichloroethanol , is responsible for most its toxicity, its low therapeutic index, and its undetectable presence in plasma.

Sings and symptoms of toxicity

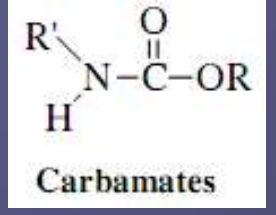
CNS depression, ataxia, gastrointestinal irritation, cardiovascular instability, and proteinuria.

An increased risk of sudden death with chloral hydrate intoxication is a result of development arrhythmias.

Chloral hydrate has been implicated as a carcinogen, this finding remains controversial.



Meprobamate

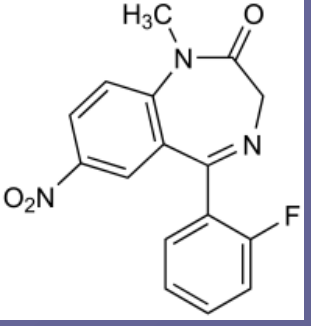


A propanediol carbamate derivative.

is marketed as an alternative S/N to barbiturates.

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.



Flunitrazepam

Is used in treatment of insomnia and anesthetic as benzodiazepine.

The tablets are tasteless, odorless , relatively inexpensive ,dissolve rapdly in alcohol, and are easily administered by intranasal or oral.

Department of justice [drug-facilitated rape].

The victim of a drug –facilitated sexual assault may exhibit singe of confusion, memory loss, drowsiness, slurred speech .and uninhibited behavior.

- The flunitrazepam causes euphoria, hallucinations and used to enhance heroin and cocaine euphoria.
- It is highly lipid soluble, with a quick onset (20-30min)

And a duration of up to 12 h.

It affects GABA receptors with a potency of up to ten times that of diazepam.

as a result ,drowsiness, disorientation, and dizziness (DDD), slurred speech, respiratory depression and coma.

Treatment is supportive, with respiratory maintenance of primary importance (ABC) (maintain airway , breathing and circulation).

Flumazenil **is used as an antidote** for respiratory depression.

GHB(gamma-hydroxybutyrate)

- Since its synthesis in 1960 GHB has been **abused for sleep disorders** , as an **anesthetic agent** , as treatment for alcohol and opiate and an **aphrodisiac**.
- The tasteless ,odorless, liquid or gel, use as a date –rape drug.
- GHB interacts with GABA-b receptors, as well as opioid receptors, depressed CNS
- It has a quick onset (15-30 min) and relatively short duration. 3 h.

Ingestion of GHB in an alcoholic drink by victim, causes hallucinations and amnesia, as will as symptoms not unlike flunitrazepam.

At higher doses in absence of alcohol ,its toxicity outweighs the euphoric effects.

Within 15 min of ingestion , the apnea ,hypoxia and vomiting, respiratory depression,bradycardia, muscal contraction ,decreased cardiac output, amnesia and coma

Apnea: انقطاع التنفس

Amnesia: فقدان الذاكرة

Outweighs: أكثر أهمية

- As flunitrazepam, treatment of GHB toxicity is supportive, with respiratory maintenance of primary importance(ABC)
- Withdrawal symptoms are important.

  Anxiety attacks, and increased blood pressure a few hours after the last dose.

Anxiety attacks: نوبة قلق

Buspirone

Buspirone is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other S/H drugs.

It does not exert anticonvulsant or muscle relaxant effects, nor does it interact with GABA receptors.

Instead, it has high affinity for serotonin (5-HT1A) and dopamine (D2) receptors.

Buspirone

-Overdoses of up to 150 times the average anxioltytic dose (approximately 3 g) have not been associated with lasting untoward effects.

-In addition, additive effects with ethanol are minimal.

It has not been associated with the production of dependence or withdrawal,

-unlike the barbiturates and benzodiazepines, buspirone is not a federally controlled substance.

Methods of detection

- Urine screening is useful for detecting many criminal drugs except flunitrazepam, which requires specific analysis.
- Because of their short half-life and low concentrations, most commercially available toxicology screens (immunoassays)are unable to detect flunitarzepam .
- The most definitive detection of flunitarzepam is GC-MS.

The immunoassays, enzyme-multiplied immunoassay technique (EMIT) and radioimmunoassay(RIA), are designed to identify unmetabolized barbital in the urine.

Positive tests for phenobarbital have been noted in chronic users up to several weeks after discontinuation.

TLC,GC,GC/ID, GC/MS,HLPC