Pharmacology

Central Nervous System Pharmacology

The CNS is very important compartment of nervous system because it is considered as a coordinator of body organs activities because its control on vital centers, this control is occur via electrochemical substances termed (Neurotransmitters).

These neurotransmitters are divided to two types according to the postsynaptic effect these transmitters: -

1- **Excitatory neurotransmitters**: - act by depolarizing the nerve cells. And include: -

- *Acetylcholine:* acts on two types of receptors in the spinal cord, nicotinic receptors and muscarinic receptors. Acetylcholine effects on arousal, short term memory and learning.
- *Glutamic and aspartic acids:* excite motor neurons in the CNS.
- Substance P: mediate the nociception (pain) within spinal cord
- *Norepinephrine:* acts on two types of receptors (α and β). Norepinephrine effects on arousal, wakefulness, mood and cardiovascular regulation.
- *Dopamine:* its effects on emotion and reward system.
- *Serotonin:* effect on the feeding behavior, control of body temperature, modulation of sensory pathways (including: nociception (pain), regulation of emotion and mood and sleep and wakefulness.

2- **Inhibitory neurotransmitters**: - act by hyperpolarization of the nerve cell.

- *GABA (γ – amino butyric acid)* is the major inhibitory neurotransmitter in the mammalian CNS, its inhibits the presynaptic neuron.
- *Glycine:* is another inhibitory CNS neurotransmitter whereas GABA is located primarily in the brain glycine is found predominantly in the ventral horn of the spinal cord.
- *Encephalins and Endorphins:* they are having morphine like effect in controlling pain and producing addiction.

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CNS drugs is either depressant or stimulant: -

 CNS stimulants: are drugs that increase behavioral activity, thought processes, and alertness or elevate the mood of an individual. It's also called analeptics and are classified as:

1. Medullary stimulants:

- They stimulate centers in the medulla oblongata
- The main therapeutic use of these drugs is to neutralize the depressing effect of CNS depressants like anesthesia. or in treatment of antiepileptic agents abuse.
- E.g. Leptazole, Nickthamide, Bemigride, Doxapram Ethamivan, Amiphenazole, Picrotoxin and Camphor.

2- Central stimulants:

+ Drugs stimulate the cerebral cortex therefore they called central stimulants, the most important group are xanthine derivatives which characterized by the following:

- Stimulate heart and blood vessels directly and indirectly increase blood flow in the brain and kidney causing increasing urine production (diuresis).
- Promote prothrombin production in the liver (Vit. K like action).
- The most commonly used agents of this group are caffeine derivatives (coffee, tea, and cocoa.
- Another xanthine derivatives is theophylline which has similar in action of caffeine and its more potent cardiac stimulant and diuretic, it's used mainly as bronchodilator.

3. Spinal stimulants:

This type of stimulants affects the spinal cord the most used drug for this purpose is strychnine (an alkaloid derived from *Strychnos nux vomica* seeds, which are still used in homeopathic medicine. It is a colorless crystalline alkaloid and is extremely bitter in taste. It is also a very toxic substance having a median lethal dose (LD_{50}) of approximately 10 mg, and its cause the following clinical signs:-

- Awful, bitter taste
- Clonic-tonic convulsions
- Dilated pupils
- Hyperreflexia
- Mind and consciousness are maintained
- Death results due to asphyxia or exhaustion.

CNS depressants:

Central nervous system depressants are medications that suppress the transmission of information throughout the central nervous system. The degrees of CNS depression are graduating from mild depression (sedative – hypnosis) to complete CNS depression (general anesthesia), and this degree depends on:-

1- The used drug.
2- The dose
3- Animal species
4- Combination.

1. **Sedative-hypnotics**: are commonly referred to as sedatives and is the mildest form of central nervous system depressant.

- Sedative-hypnotics are given in low doses to diminish the patient's physical and mental responses without affecting the patient's consciousness.
- With increased doses, the patient experiences a hypnotic effect causing the patient to fall a sleep.
- Even higher doses of sedative-hypnotics anesthetize the patient. Such is the case of the ultra-short-acting barbiturate thiopental sodium (Pentothal) that produces anesthesia.

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Benzodiazepines: All benzodiazepines in clinical use have the capacity to promote the binding of the major inhibitory neurotransmitter γ-amino butyric acid (GABA) to GABA receptors (GABA potentiators).

- This group of drugs is widely used in induction of the state of hypnosis and when given by high doses it can promote other degrees of CNS depression like tranquilization and anticonvulsion.
- The most clinically used members of this group are Diazepam (Valium), Nitrozepam (Mogadon) and Clonazepam (Rivotril).

Barbiturates: derivatives of 2, 4, 6-trioxohexahydropyrimidine that reversibly depress the activity of all excitable tissues. This Group of drugs is effect on the CNS by the following ways:-

1. Its minimize O_2 utilization by the brain.
2. Preventing the synthesis of Ach. (Block the conversion of pyruvate to acetate).
3. potentiating the inhibitory neurotransmitter GABA (similar to mechanism of action benzodiazepines).

Barbiturates can be classified according to the duration of action to:-

- ***Ultrashort-acting barbiturates:***- acts within seconds and has a duration of action of about 30 minutes. such as thiopental sodium (Pentothal) are a commonly used anesthetic.
- ***Short-acting barbiturates*** such as Secobarbital (Seconal) and pentobarbital (Nembutal) are short-acting barbiturates that induce sleep. For longer periods of sleep, patients are prescribed.(3–8 Hours).
- ***Intermediate acting barbiturates*** such as amobarbital (Amytal), aprobarbital (Alurate) and bubatabarbital (Butisol). For longer periods of sleep.
- ***Long-acting barbiturates*** such as Phenobarbital and mephobarbital are used for controlling epileptic seizures, has a duration of action greater than a day.

 Barbiturates are Controlled Substances and should be prescribed for no more than two weeks because of the adverse side effect. Barbiturates increase CNS depression in the elderly and should not be used for sleep.

 Side effects of barbiturates include: Drowsiness may last for only a few hours after a hypnotic dose of barbiturate, but residual CNS depression sometimes is evident the following day, and slight distortions of mood and impairment of judgment.

Residual effects also may take the form of vertigo, nausea, vomiting, or diarrhea or sometimes may be manifested as overt excitement. The user may awaken slightly intoxicated and feel euphoric and energetic; later, as the demands of daytime activities challenge possibly impaired faculties, the user may display irritability and temper. Over dose of barbiturates can cause respiratory failure due to depression of respiratory centers.

2. Tranquilizers: drugs which produce in an animal a state of indifference to its surrounding.

+ Tranquilizers are used to:-

 Facilitate the control of difficult animals of all species.

 Pre-anesthetic drug to reduce the amount of required anesthesia in order to minimize risk of toxicity, and to help in induction of anesthesia.

Phenothiazine derivatives:

 The phenothiazines block post-synaptic dopamine receptors in the CNS and may also inhibit the release of, and increase the turnover rate of dopamine.

 They are thought to depress portions of the CTZ (chemoreceptor trigger zone) which assists in the control of body temperature, basal metabolic rate, emesis, vasomotor tone, hormonal balance, and

alertness. Additionally, phenothiazines have varying degrees of anticholinergic, antihistaminic, antispasmodic, and alpha-adrenergic blocking effects. (hypotensive effect).

- The main drugs of this group are:- chloropromazine, trimeprazine, methotrimeprazine, acepromazine, promazine and promethazine.

Butyrophenones:

- They have similar pharmacological effects to phenothiazines with rapid onset of action (10 min.)
- They have hypothermic and α blocking actions with powerful antiemetic action.
- E. g. droperidol, haloperidol and azaperone.

Benzodiazepines:

- According to the used dose, benzodiazepines can use as tranquilizers.
- There mode of action was discussed previously.
- The most used drugs from this group are diazepam which given with morphine and its derivatives to avoid excitation and zolazepam which mixed with Tiletamine (an injectable anesthesia chemically related to ketamine) to control the exotic animals especially during transport.

3. Anticonvulsants (antiepileptic):

Epilepsy: is a common neurological abnormality Epilepsy is a chronic, usually life-long disorder characterized by recurrent seizures or convulsions and usually, episodes of unconsciousness and/or amnesia, Patients often exhibit more than one type. In most instances, the cause of the seizure disorder is not known (idiopathic epilepsy), although trauma during birth is suspected of being one cause. Head trauma, meningitis, childhood fevers,

brain tumors, and degenerative diseases of the cerebral circulation are conditions often associated with the appearance of recurrent seizures that may require treatment with anticonvulsant d rugs. Which are:-

Barbiturates: long acting barbiturates are very useful in controlling of these seizures like Phenobarbital; overdoses can cause death due to respiratory failure.

Phentoin: a hydontoin- derivative it depress the CNS through increasing the ionic efflux (Na^+) from neurons.

Primidone:

- An analog of Phenobarbital.
- Its indicated for seizures.
- Its safer than Phenobarbital because it's less hepatotoxic.
- Its used to control convulsion in foals.

Valproates: salts of valproic acid. They prevent degradation of GABA. and they are very important anticonvulsants.

Benzodiazepines: they are very useful agents in treating deferent forms of epileptiform convulsions, and they are used as alternative medicines to barbiturates.