Drugs acting on CNS

The drugs that affect CNS act by altering some steps in neurotransmitter process

Act either in presynaptic through influencing the production, storage and release and termination of neurotransmitter.

Or post synaptic receptors through activation or blockage these receptors

Sedative, hypnotics and anxiolytics

Anxiolytics: the drugs that relief anxiety with little CNS depression

Sedatives: the drugs that quite the excited or agitated patient

Hypnotics: the drugs that induce sleep and useful in the treatment of insomnia

Drugs in this group include benzodiazepines, barbiturates, buspirone, chloralhydrate, meprobamate

Other drugs include beta-blockers and H1-antihiatamines

Benzodiazepines:

Examples: diazepam, lorazepam, temazepam and nitrazepam , chlordiazepoxide, oxazepam. All these drugs act by the same mechanism and only differ in pharmacokinetics parameters as the half-life and route of metabolism

BZD was replaced the barbiturate and meprobamate in treatment anxiety because BZD are safer and more effective.

Mechanism of action

The benzodiazepines are similar in chemical structure to the inhibitory neurotransmitter gama amino butyric acid (GABA), an inhibitory neurotransmitter. They act by binding to the benzodiazepine site at the GABA receptors which lead to the opening of chloride ion channels and the potentiation of the action of GABA. So benzodiazepines potentiate the actions of GABA. There are different sub-types of benzodiazepines receptors which mediate different actions. Benzodiazepines act on the brain reticular system and the limbic system.

Benzodiazepine antagonist as flumazenil can also combined with benzodiazepine receptors and antagonizes all the actions of benzodiazepines.

Pharmacokinetics of benzodiazepines:

Well absorbed when given orally. The absorption of intramuscular injection is less rapid and irregular, so it is not preferred to be given by this route while the intravenous injection produces rapid effect and useful in emergency.

The benzodiazepines are highly protein bound (85%).

The major site of metabolism is the liver, the metabolism include chemical biotransformation followed by conjugation with glucuronide to be excreted in the urine.

Liver disease lead to reduce rate of metabolism and increase toxicity in which case **lorazepam** and **oxazepam** are preferred as they metabolized by conjugation only.

Most of the metabolites of benzodiazepines are pharmacologically active and this lead to prolongation of their pharmacological action. The metabolism of benzodiazepines decrease with age, so the dose should be reduced in the elderly patients. Also the dose should be reduce in patients with liver disease

Clinical uses of benzodiazepines:

- anxiety and panic state: both acute and chronic anxiety can be treated with benzodiazepines , the lowest effective dose should be used for the shortest possible time to avoid tolerance and dependence, drugs used include diazepam, chlordiazepoxide and lorazepam
- Insomnia (difficulty to go to sleep), benzodiazepines reduce the latency to sleep and prolonged the sleeping time. They reduce rapid eye movement (REM) sleep but to lesser extent than other hypnotics. Drugs with shorter half life as nitrazepam are preferred to avoid prolonged sedation
- muscle relaxation, due to inhibition of polysynaptic reflexes in the spinal cord, they are especially useful in pain and muscle spasm associated with injuries and inflammatory condition, diazepam is usually used. Benzodiazepines are also useful in tetanus to relief muscle spasm

- anticonvulsants in status epileptics and in febrile convulsions in children, usually given intravenously or rectally as diazepam or lorazepam
- In epilepsy as antiepileptic, like clonazepam which is useful in some form of epilepsy specially in children
- pre-anaesthetic medications to reduce anxiety before surgical operations and to produce anterograde amnesia (loss of memory after drug administration) for the procedure
- Alcohol and hypnotics drug withdrawal state, to relief the symptoms of withdrawal as chlordiazepoxide and diazepam

Adverse effects of benzodiazepines:

- on the central nervous system , cause sedation, drowsiness, ataxia and amnesia, slowing of reaction time impair driving skill and predispose for accidents
- rapid intravenous injection may lead to respiratory and cardiovascular depression which may be fatal in patients with cardiac or respiratory diseases
- dependence and tolerance: prolonged use of benzodiazepines can lead to both physical and psychological dependence and withdrawal symptoms (occurs when the patient suddenly stops taking the drug) characterized by severe anxiety, insomnia, tremor and convulsions associated with nausea, vomiting and loss of appetite. It is therefore recommended that these drugs stopped gradually by dose reduction with time specially after prolonged use

- Overdose lead to CNS and respiratory depression followed by coma, which is much less sever than barbiturate. Benzodiazepines rarely cause death in overdose when ingested alone, but death might occur when taken with other CNS depressant drugs
- Drugs interaction, benzodiazepines Potentiate the effect of other CNS depressants as alcohol, antihistamines and barbiturates.

Flumazenil

- Is a benzodiazepine antagonist, acts by binding to benzodioazepine receptors it can reverse the effects of benzodiazepine overdose and toxicity. It should be given by intravenous injection. Usually repeated doses are needed because it has a short half-life. Can also be used to terminate the benzodiazepines action when used in endoscopy and intensive care.

- Flumazenil can precipitate withdrawal symptoms in benzodiazepines dependent patients and it may cause convulsion, so should be given with caution in these patients. It may cause brief anxiety.

Barbiturates

Example; phenobarbitone, primidone, pentobarbitone and thiopentone

- Mechanism of action: Like benzodiazepines enhance the action of GABA, but they bind to different sites on the GABA-receptors/chloride channels, and there action on the CNS is less specific lead to more CNS depression

Barbiturates are less commonly used as hypnotics, sedatives or anxiolytics

because:-

1. Barbiturates has low therapeutic index (can cause respiratory and cardiovascular depression even when given even therapeutic doses)
2. Can rapidly cause strong physical dependence with withdrawal symptoms
3. They are potent enzyme inducers which lead to wide interaction with other drugs
4. Highly toxic in overdose and frequently lead to death due to respiratory and CNS depression

Pharmacokinetics:

Rapidly absorbed after oral administration with variable plasma protein binding, are metabolized by the liver and can induce hepatic drug metabolizing enzymes

Clinical uses:

- epilepsy as antiepileptic in tonic-clonic epilepsy (oral phenobarbitone and primidone)
- induction of anesthesia (I.V thiopentone), to make the patient unconscious quickly. **Thiopentone** is highly lipid soluble and acts within seconds when given intravenously
- neonatal jaundice, as enzyme inducer (oral phenobarbirtone), which induce the liver enzymes, so increase bilirubin conjugation to water soluble compound and enhance it renal excretion

Adverse effects:

- hypotension and reduction of cardiac output and myocardial depression
- drowsiness, dizziness and confusion
- respiratory depression especially in patients with asthma and bronchitis
- physical and psychological dependence with withdrawal symptoms as tremor, weakness , dizziness, distorted vision, delirium and convulsions in severe cases
- Allergic reaction as skin rash
- drug interactions; potentiate the effect of other CNS depressants and also induce metabolism of other drugs and reduce their effects

Meprobamte

Have sedative, hypnotic and anxiolytic effects. May cause excessive sedation and dependence liability, so it is less used in anxiety.

- **mechanism of action** is not known. ... **Meprobamate** binds to $GABA_A$ receptors which interrupt neuronal communication in the reticular formation and spinal cord, causing sedation and altered perception of pain
- P/K:- It is absorbed well when given orally, metabolized by the liver and has

significant enzyme inducing effect .Meprobamte is used as muscle relaxant mainly to relief muscle spasm by inhibiting spinal reflexes, due to potentiating the effect of GABA inhibitory transmitter in the spinal cord

- Adverse effects: excessive sedation, drowsiness, dependence and Withdrawal symptoms lead to insomnia, anxiety and convulsions

Chloralhydrate

- is used mainly as hypnotic to induce sleep as it is given orally as solution to reduce gastric irritation and improve its bad taste. It induces sleep within half hour of oral dose. It is relatively safe in therapeutic dose but in high doses causes respiratory depression.
- Chloralhydrate absorbed well from the intestine, metabolized by the liver into trichloroethanol (the active form of the drug) by the action of the enzyme alcohol dehydrogenase. Used mainly as hypnotic especially in children.
- It interacts with alcohol because they are metabolized by the same enzyme and this will lead to inhibition of alcohol metabolism and increase its concentration and toxicity

Buspirone

- Relief anxiety with less sedative or euphoric effect. Buspirone differs from benzodiazepines in mechanism of action. Acts as partial agonist at serotonin 5HT1A and dopamine D2 receptors.
- Have minimal dependence and abuse potentials
- Has less psychomotor impairment effect in comparison with diazepam
- Fewer interactions with CNS depressant drugs
- Well absorbed from the GIT and extensively metabolized by the liver and highly bound to plasma proteins (95%)
- It is effective in anxiety but has no muscle relaxant of anticonvulsant effects and dose not potentiate the effect of other CNS depressant drugs

Zopiclone

Acts like benzodiazepines on benzodiazepines/GABA receptors. Has similar effects to benzodiazepines, causes less dependence and fewer withdrawal symptoms

Chlormethiazole

Is related in structure to vitamin B_1 (thiamine). It may acts by altering dopamine function in the brain. It is mainly useful in the treatment of withdrawal state of alcohol. It has sedative, hypnotic and anticonvulsant effects

Beta-blockers in anxiety:

Beta blockers are useful in the treatment of autonomic symptoms of anxiety as tremor, palpitation and excessive sweating. The highly lipid soluble beta-blockers as propranolol are most useful as they can pass to the brain more easily.

Anihistamines

As diphenhydramine and chlorpheneramine

H1 antihistamine has sedative effects probably not related to their histamine antagonist effect; this can be therapeutically useful when anxiety associated with allergic disease.

Their potent anticholinergic effect prevent the abuse of these drugs

Anti psychotic drugs

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Also called Neuroleptics and major tranquilizers

They are effective in the treatment of schizophrenia. They are also useful in psychosis associated with depression and mania and the

treatment of acutely disturbed patient.

Schizophrenia is characterized by; delusions (paranoid), hallucinations, thought disorders and abnormal behavior, social withdrawal and flat emotions

Schizophrenia was found to be associated with increase in dopamine activity in the brain, with possible role for 5HT, so drug useful in this disease are expected to modify these neurotransmitters

History of antipsychotic drugs

- Antipsychotic drugs have been used in Western medicine for more than 50 years.
- **Chlorpromazine (1952)** and **Reserpine** were the first drugs found to be useful in schizophrenia.
- Tricyclic and MOA inhibitor antidepressant in 1957-58.
- Major novel antipsychotics are selective serotonin reuptake inhibitor and it has been introduced in 1980s.
- Little attention was paid to Cade's report in 1949 that Lithium could be used for excitement and mania: its effective use started in the 1960s and now it has a unique place in psychiatry.

Classification of antipsychotic drugs:

1. **Phenothiazines:** chlorpromazine, promazine, promethasine, thioridazine, trifluperazine, prochlorperazine and fluphenazine
2. **Butyrophrnones:** haloperidol, benperidol
3. **Thioxanthines:** flupentixol, zuclopenthioxol
4. **Atypical antipsychotic**: pimozide, loxapine

Mechanism of action:

Antipsychotic drugs act by blocking dopamine D_2 receptors centrally in the brain, this blockade produce the antipsychotic and antiemetic effects.

The antipsychotics also inhibit the function of the hypothalamus, which cause loss of temperature control, galactorrhea, amenorrhea, and weight loss

The blockade of D_2 receptors also produce the extra-pyramidal symptoms (These symptoms include **dystonia** (continuous spasms and muscle contractions), **parkinsonism** (characteristic symptoms such as rigidity), **bradykinesia**(slowness of movement), **tremor**, and **tardive dyskinesia** (irregular, jerky movements).

The anti psychotics can also act on other receptors which include:

- alpha adrenoceptor blockade
- anti-muscarinic
- histamine-H 1 receptor blockade
- serotonin (5HT) receptor blockade

1- Phenothiazines

Chlorpromazine is the prototype of this group

Mechanism of action: They have central calming effect which inhibits hallucination (D2blockade). They also can inhibit the chemoreceptor trigger zone and the hypothalamic function. They produce powerful extra-pyramidal effects. They also have alpha-adrenoceptor blockade, this cause postural hypotension

Pharmacokinetics:

Phenothiazines have variable absorption from the gastrointestinal tract with bioavailability of only 30%. The absorption is delayed by the presence of food.

Peak plasma level reached in 2-3 hours with half-life between 2 to 24 hours.

They are highly lipid soluble with a wide volume of distribution.

They are mainly metabolized by the liver with large number of active metabolites. Phenothiazines are highly protein bound (90-95%).

Clinical uses of phenothiazines (chlorpromazine):

1. as anti psychotic in schizophrenia specially useful in acute episodes
2. hypomania
3. severe anxiety not responding to benzodiazepines and panic state
4. co-analgesic in chronic pain and terminal illness
5. anti-emetic, due to inhibition of CTZ useful in vomiting due to metabolic disturbances, cytotoxic drugs and radiations
6. intractable hiccup due to phrenic nerve irritation
7. allergic conditions as promethazine has a strong antihistamine effect
8. in the treatment of non-pyrogen induced fever to lower body temperature

Adverse effects of phenothiazines:

Anticholinergic effects; blurred vision, dry mouth, constipation, urinary retention.

postural hypotension due to blockade of α_2 adrenoceptors

excessive sedation, drowsiness and confusion and seizures

abnormal involuntary movements including tremor, dystonia and dyskinesia, this is due to blocked of dopamine effect in the brain

cholestatic jaundice occurs in 2-6% of patients as an idiosyncratic reaction

Allergic reactions; skin rash, and bone marrow suppression

Cardio-toxicity; cardiac arrhythmias and conduction block

Interaction with other drugs:

a. can potentiates the effect of other CNS depressant drugs

b. anti-cholinergic effect decrease the absorption of other drugs

c. potentiates the effect of anti-hypertensive drugs

d. they can inhibit hepatic drug metabolizing enzymes and increase the toxicity of other drugs

2- Butyrophenones:

Haloperidol:

It is used as alternative to phenothiazine as anti-psychotic drug.

Mechanism of action:

Haloperidol exhibits high affinity dopamine D_2 receptor antagonism.

The drug binds preferentially to D_2 and $\alpha_1$receptors at low dose, and 5-HT_2 receptors at a higher dose, Haloperidol's negligible affinity for histamine H_1 receptors and muscarinic M_1acetylcholine receptors yields an antipsychotic with a lower incidence of sedation, weight gain, and orthostatic hypotension.

Pharmacokinetics:

The bioavailability of oral haloperidol ranges from 60–70%, The drug is well and rapidly absorbed with a high bioavailability when injected intramuscularly while from IV injection the bioavailability equal to 100%.

Metabolized by the liver and has no pharmacologically active metabolites

Clinical use of Butyrophenones:

1. Haloperidol is used in the control of the symptoms of Schizophrenia
2. Hyperactive delirium (to control the agitation component of delirium)
3. Adjunctive treatment of alcohol and opioid withdrawal
4. Treatment of severe nausea and emesis in postoperative and palliative care, especially for palliating adverse effects of radiation therapy and chemotherapy in oncology
5. Treatment of intractable hiccups

Adverse effects of Butyrophenones :

Common Extrapyramidal side effects including:

- •Dystonia (continuous spasms and muscle contractions)
- •Muscle rigidity
- •Parkinsonism (characteristic symptoms such as rigidity)

•Hypotension(less than Phenothiazines)

•Anticholinergic side effects such as

- •Constipation
- •Dry mouth
- •Blurred vision

•Haloperidol can also cause leukopenia,

•a granulocytosis and jaundice

3-Thioxanthene

The derivatives of thioxanthene used clinically as antipsychotics include:

Chlorprothixene, Clopenthixol, Flupenthixol, Zuclopenthixol

The therapeutic efficacy of these drugs is related to their ability to antagonize the D_2 receptors in the brain.

They have actions at other sites such as serotonin, adrenaline, and histamine receptors as well which mostly contribute to side effects.

Flupentixol

Clinical use and the pharmacokinetics

flupentixol main use is as a long-acting injection given once in every two or three weeks to individuals with **schizophrenia** who have poor compliance with medication and suffer frequent relapses of illness, though it is also commonly given as a tablet.

Adverse effects

- Extra pyramidal side effects
- Anticholinergic side effects
- Hyperprolactinemia and its complications such as:-

- Sexual dysfunction, Amenorrhea, Gynecomastia, Galactorrhea

4-Atypical antipsychotic drugs:

Clozapine, Olanzapine, Resperidone.

Mechanism of action

Atypical antipsychotics have weak D2 and potent 5HT2 and alpha antagonist properties

Also have antihistamine and anticholinergic and rarely cause extrapyramidal symptoms.

Clinical use

Clozapine use for schizophrenia only because risk of a granulocytosis, while Olanzapine for schizophrenia and mania.

Adverse effects

Clozapine

Sedation, seizure, weight gain and hypotension and a granulcytosis therefore need frequent monitoring for blood account.

Olanzapine

Dry mouth, constipation and rarely EPS and No a granylcytosis.