

**SHIVAKANT SHUKLA**

**LNCP,BHOPAL**

REFFER ALREADY SHARED NOTES FOR STRUCTURE, SAR AND GIVEN SYNTHESIS ONLY

 STAY HOME, STAY SAFE, GOOD LUCK

 Hypnotics are drugs which induces a state resembling natural sleep from which the person is arousable by the external stimuli.

 Hypnotics in small doses are sedatives since they

induces the calmness without inducing sleep.

 Sedative agent should reduce the anxiety and exert the calming effect.

 Hypnotic involve more pronounced depression of CNS

than sedatives.



 **REM SLEEP: FAST WAVE EEG SLEEP**

 Awakened subjects state they were dreaming.

 Heart rate ,bp,respiration are fluctuant, cerebral blood flow increased,skeletal muscle profoundly relaxed.

## NREM SLEEP:SLOW WAVE EEG SLEEP..

 Awakended stage they were dreaming...

 Heart rate respiration bp are fluctuant,...

 Growth hormone secretion maximal and sleep restful.



 wakefulness---sleep latency—into nrem sleep

 initial hour of nrem sleep(90 minute)--- 20 minute rem sleep (ie. 4 cycles)

 **STAGE 0**: awake, EEG: α activity when eye closed and β activity when open

 **STAGE 1**: dozing,α activity intersperced with θ activity.3-6% of sleep time.

 **STAGE 2** : Unequivocal sleep,θ waves with intersperced spindles,k complex can be evoked on stimulation.40-50 % sleep time

 **STAGE3:** Deep sleep transition , EEG shows the θ,δ and spindle activity K complex evoked with strong stimuli..

 **STAGE4:** Cerebral sleep, δ activity predominate in the EEG,eyes practically fixed.night terror may occur.10- 20 % of sleep.

 2,3,4 heart rate ,BP,respiration are steady...

 3 and 4 together called slow wave sleep...

 **REM SLEEP**: EEG waves are of all frequency...K complex cannot be ellicited...HR and BP fluctuate.. 20-30 %sleep time occurs in this period.....



 In ninteenth century bromide was the specific agent

introduced as sedative hypnotics...

 Chloral hydrate,paraldehyde ,urethane,and sulphone came later..

 In 1903 barbital and 1912 phenobarbital introduced.

 1950 synthesis of chlordiazepoxide by sternbach and discovery of unique pattern of action by Randall .

 Introduction of chlordiazepoxide into the clinical medicine in 1961 ushered the era of the benzodiazepines.



***CLASSIFICATION:***

 **long acting :** diazepam,flurazepam,clonazepam,chlordiazepoxi de

 **shortacting:**

alprazolam,estazolam,temazepam,lorazepam,nitr azepam

**ultrashortacting:** midazolam,triazolam,oxazepam



##  GABAA RECEPTER:

***STRUCTURE*** : Pentameric and assembled from the five subunit (each with 4 membrane spanning domains) selected from multiple polypeptide classes (α,β,γ,δ,π,ρ)

A model of GABA A Recepter mediated chloride channel 2 α,2β ,1γ subunit...



 ***CNS EFFECTS***:

 Hypnotic, sedative,anxiolytic,anticonvulsant,and central muscle relaxant actions..

 Benzodiazepines act cheifly on brain recticular activating systems,limbic system nd median forebrain bundle and hypothalamus .

 Benzodiazepine shorten the time taken to go to sleep(sleep latency),decrease intermitent awakening,and increase total sleep duration..

#  BENZODIAZEPINE ANTAGONIST:

FLUMAZENIL: Competitive antagonist at benzodiazepine recepters and some agonist action (partial agonist).. Has a t ½ of 1 hour...heavily sedated patient become alert with in 1 hour....

adverse effects:vomiting,brief anxiety,seizure in epieptics treated with benzodiazepines...



1. **To treat anxiety neurosis**: most commonly used are alprazolam,lorazepam,oxazepam,diazepam,chlordi azepoxide.

**Alprazolam** has anxiolytic antidepressant property(0.25 -.5 mg BD or TDS)

**Lorazepam** for short lived anxiety states and compulsive obsessive neuroses and tension induced psychosomatic symptoms(1-6mg per day).

1. **INSOMNIA**
2. **FOR PREANAESTHETIC MEDICATION AND INDUCTION OF ANAESTHESIA:**

 **D**iazepam,lorazepam and midazoam are generally used for this purpose ..midazolam most often used as it produces high degree of amnesia and has a more rapid onset with shorter duration of action..

 **AS SKELETAL MUSCLE RELAXANT:**

 Diazepam prefered for relaxing effect in skeletal muscle.

***DRUG INTERACTIONS:***

 Potentiate the effect of of other CNS depressant such as alcohol,hypnotics and neuroleptics.

 Smoking decreases the activity of benzodiazepines...

 Aminophylline antagonises the sedative effect of benzodiazepines.

 Enzyme inhibitors like cimetidine,and ketoconazole enhances the benzodiazepine action..

 ***ADVERSE DRUG REACTIONS* :**

**D**rowsiness,confusion,amnesia,and impaired co ordination which considerably affect the manual skill such as driving performance...



 ***PHARMACOKINETICS*** :

* Well absorbed and given orally.
* High lipid solubility ,bind strongly to plasma protein.metabollised and eventually removed as glucuronides.
* Several converted to active metabolite like nordazepam (n -desmethyl diazepam) which has a half life of 60 hours and this responsible for the cumulative effect of many diazepams.

## NEUROPHARMACOLOGY:

 GABA major inhibitory neurotransmitter in the CNS.

 Benzodiazepine seems to increase the efficiency of the GABAnergic synaptic inhibition .

 Benzodiazepines causes the enhancement in the chloride ion conductance induced by interaction between recepter and the benzodiazepines....



 **ZOLPIDEM**: Have t ½ of 2-3 hours

 Dose 10-20 mg at night time treat the transient insomnia

 **ZOPICLONE**:t ½ of 3-4 hrs

 Dose 7.5 mg to treat transient insomnia

 ZALEPLON:t ½ of 6-8 hrs

 Dose:10-20 mg

 USES: To treat short term insomnia

 Negligible muscle relaxant and anti convulsant action.

 Tolerance and dependance much less as compaired to BZDS

 Dose reduction needed in the hepatic and elderly patients



CLASSIFICATION:

 1.Long acting drugs: phenobarbitone

,mephobarbitone

* 1. Intermediate acting: amylobarbiturate,butobarbitone,
	2. Short acting drugs: secobarbitone,pentobarbitone
	3. Ultrashort acting; thiopentone...

 Mechanism of action: increase the inhibitory activity of the GABA and GABA mediated increase in chloride conductance.

 Barbiturate potentiate the acction of benzodiazepine probably by addictive effect



 **1.CNS DEPRESSION**: Mild to profound central nervous system depression and death due to the depression of the vital medullary center including the cardiovascular and respiratory center .

Respiratory depression can occur in hypnotic doses in chronic lung patients ...

## 2.OTHER SYSTEMS:

**CVS**: Lower the blood pressure by reducing the cardiac output..and inducing the venodialatation.

Higher doses depresses the vasomotor center and induces the marked hypotension..



 Mostly suicidal OR accidental

 Characterised by respiratory failure,cardiovascular collapse,coma,renal failure.

 Treatment include gastric lavage,artificial respiration and forced alkaline diuresis with mannitol and sodium bicarbonate.

 In alkaline urine barbiturate get ionised and hence their tubular reabsorption is prevented thats why excretion promoted...



 MECHANISM OF ACTION:act on the channel modulatory site of the GABA A Recepter and potentiate the GABA mediated inhibitory effects by the increasing duration of the chloride channel opening.

Higher concentration directly increases the chloride ion conductance..it has a GABA mimetic action ....

 **PHARMACOKINETICS:** rate of absorption depends on the ir lipid soubility...Ph of sodium salts usually alkaline...

 Route of administration : slow i/v or orally or at times rectally

 Volume of distribution depends upon the lipid solubility..

 The action of ultra short acting barbiturate usually terminated by the redistribution.

##  THERAPEUTIC USES:

 1. **Sedative hypnotics**: seldom used now , previously short acting barbiturate used.

 2.**Anesthesia**: ultra short acting barbiturates (thiopental sodium ) as inducing agents...

 3.**Anticonvulsants**: long acting barbiturates as phenobarbitone..

 4.To treat hyperbilirubinemia of neonates as it increases its activity..



 **RAMELTEON:** It is MT1 and MT2 melatonin receptor agonist introduced in USA and now approved in India as well as a new class hypnotic for sleep onset insomnia.

 Dose: 8 mg half hour before going to bed.

 It shown to hasten sleep onset and increase in sleep duration..



 **BUSPIRONE:**

 Partial agonist primarily at the brain 5HT1A Receptors .

 So by selective activation of the inhibitory presynaptic 5HT1A recepter they suppresses 5HT neurotransmission through neuronal system

Drug buspirone is used in anxiety state (5-10 mg TDS).

Usual anxiolytic action of buspirone is delayed for two weeks which make it unsuitable for the management of the acute anxiety state.

Minimal abuse liability and elicit no rebound phenomenon like rebound anxiety and insomnia..

.

**PROMETHAZINE**:sedating antihistamine with antiemetic anti cholinergic property.

 **HYDROXYZINE**: antihistamine with sedative hypnotic action are promoted for treating insomnia.

 **TRICLOFOS:**for short term management of insomnia

 REFFER ALREADY SHARED NOTES FOR STRUCTURE, SAR AND GIVEN SYNTHESIS ONLY

 STAY HOME, STAY SAFE, GOOD LUCK

