CNS

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Pharmacology

Sheet (8)

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New Benzodiazepine Receptor Agonists:

- Because of the tolerance, dependence and addiction that are produced by benzodiazepines and because they should not be used more than 3 weeks, scientists have developed a new other drug (new relative to barbiturates and benzodiazepines).
- They are hypnotic agents that act on the same receptors as benzodiazepines, which are chloride channels, but in different subunit, benzodiazepines bind to α_1 while these new drugs (the Z drugs) are binding to α_1 subunit.
- Nonetheless, it has no anticonvulsant (antiepileptic) effect, no muscle relaxation, and no anxiolytic, they only produce hypnosis effect.
- These drugs have only one indication which is hypnosis, so they have the approval toward insomnia.
- Currently it is the most frequently prescribed hypnotic drug in the United States. They one of the best-selling drugs in the world where 20% of population is suffering from insomnia.
- It shows minimal withdrawal effects and little or no tolerance effect occur with prolonged use.
- Although zolpidem potentially has advantages over the benzodiazepines, clinical experience with the drug is still limited.
- Adverse effects include nightmares, agitation, headache, daytime drowsiness, hangover (sleep during the day) and **sleepwalking** (it as a typical type of side effects).
- There are some sort of different roots of dynamic between males and females, side effects are more in females, so we reduce the dose of zolpidem (from 10mg to 5mg) to reduce the side effects (especially the daytime drowsiness), producing the same activity.
- Z drugs include: zaleplon, zolpidem and zopiclone.
  1. **ZOLPIDEM:**
     - The only one that is present in Jordan.
     - Prescription is required, because some people knew that it has an inhibitory activity, and they abused the drug.
     - Its plasma t1/2 is ~2 hours, if you dose the patient more than the elimination of the half-life (10 mg for men, 5 mg for women), it will take a long time until the drug gets out of the body. So, we dose 4 times more than the eliminating half life to cover most of a typical 8-hour sleep period.
     - It is presently approved for bedtime use only.
     - It is good for initiating the sleep and keeping the patient in a good sleep for 8 hours.
  2. **ZALEPLON:**
     - Its plasma t1/2 is ~1 hours.
     - approved for use immediately at bedtime or when the patient has difficulty falling asleep after bedtime.
  3. **Zopiclone:**
     - Half life less than 1 hour.
     - Approved for induction of sleep (half life is enough).
     - It doesn't help the patient to sleep for long periods.
- if the patient has a problem with the induction of sleep zopiclon will work, but if the patient's problem is the inability to sleep for long periods, zelpidem is a good choice.
- Zaleplon and zolpidem are effective in relieving sleep-onset insomnia (zolpidem works for longer time). Both drugs have been approved by the FDA for use for up to 7-10 days at a time.
- Zaleplon and zolpidem have sustained hypnotic efficacy **without occurrence of rebound insomnia** on abrupt discontinuation(important).
- Zolpidem is consumed longer before bedtime than zaleplon.

- Hangover is more in zolpidem than in zaleplon; because of the longer half life (it stays more in the body).

Melatonin Congeners:

- Origin of sleep start from closing your eyes, producing melatonin which will produce an activity toward GABA producing inhibitory activity in the pineal gland.
- Two GPCRs for melatonin, MT1 and MT2, are found in the suprachiasmatic nucleus, each playing a different role in sleep, when melatonin binds to these receptors neuronal producing activities toward GABA pathway which is going to open chloride channels producing inhibitory activity (sleep).
- Binding of Melatonin to MT1 receptors promotes the onset of sleep. In case of insomnia, we look toward MT1.
- Binding of Melatonin to MT2 receptors shifts the timing of the circadian system. Responsible for the changes, induction and inhibition of circadian rhythm.
- If we lose the circadian rhythm, melatonin is used to reproduce it by targeting MT2.
- **RAMELTEON:**
  - Synthetic tricyclic analog of MELATONIN.
  - It was approved for the treatment of insomnia, specifically sleep onset difficulties (MT1).
  - Better activity in term of sleep onset difficulties.
  - **Mechanism of action:** Melatonin levels in the suprachiastmatic nucleus rise and fall in a circadian fashion -> concentrations increasing in the evening as an individual prepares for sleep, and then reaching a plateau and ultimately decreasing as the night progresses, so we try to replace this decreased melatonin by either melatonin or ramelteon.
- Melatonin (as a drug) and ramelteon both bind to MT1 and MT2 without specificity, producing a good onset of the sleep and recycling of the circadian rhythm.
- Melatonin doesn't work every time; because not all who have insomnia with have melatonin deficiency (works in 30-40% of patients).
- Melatonin is excellent for jetlag (problem in circadian rhythm).

Orexin antagonist:

- In brain, histamine and orexin work opposite to the GABA in level of producing sleep, they are responsible for wakefulness.
- Antihistamine produces sleep (مش دايمًا)
- **Suvorexant:**
  - inhibits the effect of orexin by acting as a receptor antagonist of one or both of the orexin receptors, OX1 and OX2. These receptors are the biological targets of the endogenous wakefulness-promoting orexin neuropeptides orexin-A (binds to OX1) and orexin-B (binds to OX2).
  - Medical applications include treatment of sleep disorders such as insomnia.
  - It may work and may not (as melatonin).
  - Side effects of orexin receptor antagonists include somnolence, daytime sleepiness and sedation, headache, abnormal dreams, fatigue, and dry mouth. The more the does (more than the side effect limit which is 20 mg), the more the side effects produced.
  - Modest activity (less effective than Z drugs and benzodiazepines). We can't increase the dose to give better activity, because side effects will increase also.
  - Fatigue and somnolence occur in 6-7% of patients, even in dose of 5-10 mg.

Buspirone:

- Is useful in treatment of generalized anxiety disorders and has efficacy comparable to benzodiazepines. SSRI is the best in the level of anxiety.
- In acute phase we use benzodiazepines for 1-2 weeks, then buspirone for 2-3 weeks (to bridge on), then we continue with SSRI.
- Can be used for long periods and with SSRI when it is not very effective, where it doesn't increase serotonin levels, so doesn't cause serotonin syndrome.
- It is used in case of sexual dysfunction because of SSRI, we reduce the dose of SSRI (sexual dysfunction is dose dependent) and replace this reduction by buspirone.
- Its action is mainly mediated by serotonin (5HT) receptors, increasing the inhibitory activity of 5HT receptors (agonism).
- The anxiolytic effects of buspirone may take more than a week to become established (the maximum effect after 2-4weeks), making the drug unsuitable for management of acute anxiety states (not very effective in panic disorders).
- buspirone lacks anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation and no withdrawal.
- The frequency of adverse effects is low, the most common effects being headaches, dizziness, nervousness.