Hypnotic Agents/ Antianxiety Agents

Blanton

SLIDE 1: Our focus this afternoon is on Hypnotic and Anxiolytic drugs. Hypnotic and anxiolytic agents are frequently one and the same, so we will be considering them together in this lecture.

SLIDE 2: Hypnosis, in this context, simply refers to the state of drowsiness and/or facilitation of the onset and maintenance of sleep. Hypnosis is a state from which the patient can be aroused.

Hypnotic agents are prescribed routinely in this country for the treatment of insomnia.

SLIDE 3:

-I should first point out that the SSRI antidepressants (like fluoxetine) and SNRI antidepressants (like venlafaxine) are first line treatment for most anxiety disorders. However, since we will cover those in my lecture on antidepressants, today we will focus on other anxiolytic/hypnotic agents

Of the ant anxiety drugs marketed today, many are also used as hypnotics. These drugs reduce tension, nervousness, fear, and apprehension.

Often for a single agent, one dose is used at bedtime for hypnosis, while a reduced dose is employed during the waking hours as an anxiolytic.

SLIDE 4: First, lets consider insomnia:

Insomnia is a very common medical complaint, and causes are numerous.
Short term insomnia: usually results from a stressor, such as grief, illness, or job related problems.

Long term insomnia: may result from many causes, and medical evaluation is necessary. For example, psychiatric illness, such as depression may be a cause. Illness such as asthma or COPD can create problems. Some patients think that they haven't slept, when they really have. They may think that they aren't rested enough or they may think that they haven't slept long enough. Elderly individuals tend to sleep several times per day instead of once per day. Or, they may sleep less each night than they did when they were younger. Sleep apnea produces less restful sleep.

SLIDE 5: The majority of Hypnotic agents that are prescribed do not produce a completely normal state of sleep. The vast majority of l hypnotics currently in use can create problems for the patient, so these drugs must be used judiciously.

Hypnotics reduce the latency to sleep that is they reduce the amount of time required for the patient to fall asleep. Alteration of both REM and nonREM sleep are caused by hypnotics. The older agents, the barbiturates, as well as ethanol, strongly depress REM sleep. Benzodiazepines depress REM sleep to a much smaller degree than barbs, and strongly reduce stages 3 and 4 of nonREM sleep.

After 1 or more weeks of continued administration, some tolerance develops to the effects on sleep stages.

SLIDE 6: Hypnotic agents loose their effectiveness in producing hypnosis in a matter of weeks. Barbiturates lose their effectiveness within 2 weeks, whereas benzodiazepines lose their effectiveness over a matter of 4 to 6 weeks.

Rebound REM sleep occurs after REM is suppressed for a while. This occurs when the patient discontinues the medication. The result is even more sleep disturbances, such as nightmares, etc.

Rebound REM episodes and the resultant problems that they cause are a factor in producing psychological dependence to hypnotics.

SLIDE 7: Rebound insomnia following discontinuation of the drug can occur. This insomnia also promotes the feeling of continued need for the drug. Slow tapering off of the drug is typically advised to minimize these effects.

SLIDE 8: Before we discuss barbiturates and benzodiazepines individually, I'd like to cover what is believed to be their main site of action, the gamma amino-butyric acid type A or GABAA receptor. GABA as you know is the primary inhibitory neurotransmitter in the brain. Actually the brain has high levels of GABA relative to other neurotransmitters. For example, the amount of GABA in the brain is 100 to 1000 fold greater than monoamines. GABA acts at 3 types of receptors: the GABA A, B, and C receptors. All three are inhibitory, but the type A is the only one of significance for hypnotics.

SLIDE 9: The GABAAR is inhibitory because it hyperpolarizes neurons. When GABA binds to the GABAAR, the channel associated with the receptor opens, allowing chloride ions to flow through. This net increase in negative ions intracellular pushes the membrane potential to more negative levels as is seen here. In the presence of GABA, this theoretical neuron is hyperpolarized fro its resting membrane potential of -70 mV to -90 mV. At more negative potentials, it will be less likely to fire. In contrast, in the presence of a drug that blocks the pore of the GABAAR channel, such as picrotoxin, the GABAAR inhibitory tone is reduced. The neuron's RMP is will become less negative, closer to the action potential threshold, and thus more likely to fire.

SLIDE 10: What is the GABAA receptor? It is a macromolecular complex made up of 5 subunits, a pentamer, that come together in the plasma membrane to form a central pore through which chloride ions pass. The ligand recognition site for GABA is in the N-terminus of the protein which rises above the extracellular surface of the plasma membrane.

To date 6 alpha, 4 beta, 3 gamma, 1 delta, 3 rho, and 1 epsilon subunits have been identified. That means the theoretical number of subunit combinations for this pentameric subunit complex is

staggering. However, this combination number is limited by the fact that not all subunits are present in the same brain regions. Some are localized to discrete areas, and some are present in very small amounts.

SLIDE 11: The average GABAA receptor is probably composed of alpha, beta, and gamma subunits.

(1)The site for GABA binding is located in the extracellular portion of the receptor, at the interface of the alpha and beta subunits (Panel A and B, Green). The site for binding of the benzodiazepines is at the interface of the alpha and gamma subunits (Panel A and B, Blue) .

GABA and benzodiazepines do not bind to the same site on the receptor! *However the benzodiazepine site at the alpha/gamma subunit interface is structurally homologous to the agonist site at the alpha/beta subunit interface*.

(2) Barbiturates do not bind to either the site occupied by GABA nor the site that binds benzodiazepines. There are separate binding sites for each of these agents.

- I can now say with confidence (2013) that the location of the barbiturate binding site has been identified, there are two binding sites located at the interface of the α/β and γ/β subunits within the transmembrane domain (point to Panel A and Panel C, red barbiturate).

Just a reminder - you may recall that I mentioned earlier that the binding site for general anesthetics, that is etomidate, propofol as well as Alcohol…is located in this same region of the transmembrane domain of the GABAAR, but as you can see here (Panel C, etomidate is brown) at the interface of the β/α subunits.

Getting back- While barbiturates and benzodiazepines bind to separate sites, they both enhance or potentiate the effects of GABA.

SLIDE 12: Let's consider individual agents and begin with the barbiturates. While the barbiturates were the primary agents for

hypnosis for many years, for the most part they have been replaced by the benzodiazepines, which are far safer. None the less, in case you're stuck on a desert island and only have barbiturates available to you……

Barbiturates can be conveniently divided into 3 classes based on the half-life: the long acting barbs, such as Phenobarbital; short to intermediate acting (e.g. secobarbital); and ultrashort acting (thiopental).

SLIDE 13: With respect to their pharmokinetics, they are given almost all routes. However, for their sedative-hypnotic effects, they are generally given orally. Oral absorption is good, and onset of action occurs within 10 to 60 minutes. The barbiturates are weak acids that possess varying degrees of lipophilicity. Acidosis favor the protonated (uncharged) form of the drug, thus increasing the accessibility of the drug to the CNS (crosses the BBB better). Barbiturates are distributed widely and easily cross the placenta.

SLIDE 14: The ultrashort acting barbiturates are the most lipophilic and the termination of their CNS action is by redistribution. A good example of this is thiopental. Thiopental is also metabolized, but its redistribution from the brain to other tissues accounts for its short anesthetic and hypnotic/sedative action. Most of the other barbiturates are primarily eliminated by metabolism. Oxidation, desulfuration, glycosylation, and N-hydroxylation are all examples of Phase I metabolism of the barbiturates. They are then glucuronidated and excreted by the kidney. Phenobarbital is less metabolized than other barbiturates. Between 25-50% of unchanged Phenobarbital is excreted in the urine.

SLIDE 15: Barbiturates enhance or potentiate the actions of GABA at therapeutic doses, and actually act as a GABA mimetic at higher doses (that is at high concentrations, barbiturates directly open the GABAAR channel).

EXPLAIN: This is illustrated in this slide: the graph depicts the actions of GABA and barbiturate on the GABAAR. The x-axis represents concentrations of GABA or barbiturate, and the y-axis is a

measure of the chloride ion flux through the channel and is represented as the percentage of the maximum response or current observed with GABA.
The dark blue line represents the amount of chloride flux seen with increasing concentrations of GABA. If we add pentobarbital with GABA, we see that the curve shifts to the left. This means that at these lower concentrations, GABA has a greater effect on chloride flux.; pentobarbital is potentiating the effect of GABA. At higher concentrations, pentobarbital can open the channel all by itself, shown here by the light blue line. Pentobarbital at these concentrations can directly activate the GABAAR. However, the amount of channel opening never reaches that obtainable with GABA; pentobarbital is a partial agonist at these high concentrations.

SLIDE 16: To summarize, barbiturates enhance or potentiate the actions of GABA at the GABAA receptor. They do this by prolonging the amount of time the channel is open. At high concentrations, barbiturates act as GABA mimetics, can directly activate the receptor to open. In both cases, their net action is to increase chloride flux, hyperpolarize the neuron and enhance the inhibitory tone in the CNS.

SLIDE 17: The CNS effects of barbiturates are concentration dependent. At lower concentrations, they produce sedation, hypnosis, and cognitive impairment. At higher concentrations, they produce anesthesia. At toxic doses they produce respiratory depression and death. The most common cause of death from barbiturate overdose is respiratory arrest.

Continuum: sedation…..hypnosis…….anesthesia…..death

SLIDE 18: The cardiovascular effects are extremely modest. At therapeutic concentrations, there is only a slight decrease in blood pressure. At toxic doses, the depression of vasomotor centers can lead to circulatory collapse.

SLIDE 19: Barbiturates induce P450 enzymes. Therefore, they enhance their own metabolism, as well as that of all drugs that are metabolized by the P450 system. This is an extremely important point, and is a big disadvantage for using barbiturates. A patient

taking medications that are metabolized by the liver would have to have the doses readjusted after beginning barbiturate therapy. Likewise, after terminating barbiturate therapy, the patient's medications would have to be readjusted again.

SLIDE 20: Barbiturate poisoning is not as common as it use to be; perhaps in large part to the fact that they have been replaced by benzodiazepines for hypnosis-sedation. Most barbiturate poisoning is deliberate, suicide attempts. If the barbiturate is Phenobarbital, then alkalinization of the urine can promote its excretion. A significant fraction of Phenobarbital is excreted unchanged in the urine; alkalinization will result in deprotonation of Phenobarbital (promoting charged form) and enhance its excretion. If less than 24 hours have elapsed since ingestion, gastric lavage should be considered, since barbiturates reduce GI motility. In general I barbiturate poisoning, supportive treatment must be given. Respiration is affected early in poisoning, so aggressive treatment must be instituted to support respiration. Give O2. In severe poisoning, vasomotor centers are depressed-blood pressure falls, cardiac contractility is depressed, and depression of sympathetic ganglia occur. Acute renal failure occurs subsequent to shock. Circulatory collapse follows. Dopamine treatment and hemodialysis may have to be instituted. CNS stimulants are contraindicated, because they may worsen the outcome.

SLIDE 21: The benzodiazepines have largely replaced barbiturates as sedatives and hypnotics. Generally, the benzodiazepines are safer. With benzodiazepines, the therapeutic index is higher, tolerance and liability for abuse is lower, and less drug interactions occur.

SLIDE 22: A quick peak at the structures of some of the more common benzodiazepines; you should be able to differentiate each of these for the exam….ha ha only kidding.

SLIDE 23: Benzodiazepines act to modulate GABA's action at the GABAAR. The hypnotic benzodiazepines that are used are 'agonistic' ; they enhance or potentiate the action of GABA. As is illustrated in this slide, GABA mediated responses are concentration dependent; as is represented by the dark blue line. In the presence of diazepam,

a benzodiazepine agonist, the curve is shifted to the left; see pink line. That means that more chloride ions flow through the channel at a given concentration of GABA when diazepam is present. Benzodiazepines do not directly activate the channel; as the light blue line shows, at no concentration of diazepam alone is there any chloride current flow.

To repeat, hypnotic benzodiazepines, enhance or potentiate the actions of GABA, but do not directly activate the channel (they are not GABA mimetics)

Continuum: hypnosis……..sedation…

SLIDE 24: Benzodiazepines agonists stimulate GABAA receptor function by increasing the frequency of channel openings. The net effect is increased chloride influx, hyperpolarization of neuron and increased inhibitory tone in the CNS.

SLIDE 25: Benzodiazepine agonists have a number of uses that are primarily determined by the half-life of the drug.

Therefore, in most cases any benzodiazepine could be used for most indications; in other words for the most part they are interchangeable.

As a general rule, shorter acting benzodiazepines (Alprazolam or Flurazepam) are used a hypnotics. This is to reduce day time drowsiness.

SLIDE 26 An ingested benzodiazepine may be pharmacologically active, as well its metabolites. If its metabolites are active, then the parent compound and active metabolites' half-lives must be taken into consideration when prescribing a medication to a patient for a particular use. For instance flurazepam has a half-life of 2 to 3 hours, but its active metabolite has a half-life of greater than 50 hours. Continued dosing with such a drug can lead to cumulative effects of the drug. The patients taking such a drug as a hypnotic over time would have hypnotic concentrations of benzodiazepines in their

bloodstream during waking hours. Obviously, this lead to drowsiness and psychomotor impairment.

SLIDE 27: An ideal hypnotic should be relatively short-acting-that is it should help the patient fall asleep and stay asleep fro the duration of the night. Ideally, the concentration of drug or active metabolite in the body during the day should be so low that no psychomotor affects occur. Practically, even with such short acting drugs as triazolam, there are problems. Triazolam is short acting with a half-life of 1.5 to 5 hrs. It has a metabolite that is immediately eliminated. The problems are several-fold. There may not be sufficient drug present in the early morning hours, so the patient may awaken early. Secondly, the patient may experience anxiety during the daytime hours. Finally, there may be rebound insomnia upon discontinuation of the drug.

SLIDE 28: Side effects and toxicity of the benzodiazepines are mostly psychomotor and cognitive related. The sedative effects are worse in the elderly.

-The therapeutic index is so high that it is almost impossible to commit suicide with benzodiazepines alone.

-With that said- withdraw for someone addicted to benzodiazepines can necessitate medical treatment and may include seizure activity.

SLIDE 29: I'd like to point out the multiple uses for benzodiazepines. In addition to being good hypnotics, they are excellent for anxiety that occurs with or without depression. Alprazolam (Xanax) is a benzodiazepine that also has antidepressant activity and is commonly used when both disorders are concurrent. Other uses include: panic disorders, premedication for surgery, alcohol withdraw.

Benzodiazepines are very good muscle relaxants and are useful in spasticity that accompanies paralysis and neurological diseases such as MS.

SLIDE 30: Flumazenil is an antagonist of the benzodiazepine site of the GABAA receptor. It has no intrinsic activity of its own. It simply

blocks the effect of administered or ingested benzodiazepine agonists. It will reverse the effects of the administered benzodiazepine agonist, nothing more. It will not reverse the effects of barbiturates.

For a patient that has developed a dependence on Benzodiazepines, Flumazenil is typically given in small repeated doses so as not to precipitate withdraw- which often includes seizures.

SLIDE 31: Zolpidem is a new hypnotic agent: structurally it is not a benzodiazepine, but it binds to the same site as benzodiazepines. However, it doesn't bind to all GABAAR subunit combinations and so has a more restricted action.

While it is a good hypnotic; it is not an effective anticonvulsant and is a poor skeletal muscle blocker.

It produces fewer effects on REM and nonREM sleep, and is far less likely to produce rebound insomnia or daytime sedation.

It is very short acting…….

SLIDE 32: Sex and Gender-Specific Medicine:

May 15, 2013: The FDA approved lower recommended doses for Ambien (zolpidem) for women following studies that showed that women metabolize the drug more slowly (~40%) than do men, leading to increased adverse event reporting.

The mechanism behind this difference is not know. It is also likely that lower recommended doses will be approved for other non benzodiazepine hypnotics like Lunesta and Sonata.

SLIDE 33: Zalepon is also a non-benzodiazepine hypnotic with similar features as Zolpidem.

Zalepon has an even shorter half-life (1 hr). Both Zolpidem and Zalepon are used primarily to reduce sleep latency……which is why the don't affect sleep architecture significantly.

SLIDE 34: Another agent in this same class- eszopicline (Lunesta)

SLIDE 35: Chloral hydrate is an older hypnotic that is still sometimes used. It is metabolized by the liver to the active compound trichloroethanol. It has a short duration of action and it produces fewer hangovers than the barbiturates. Like the other hypnotics, it stimulates the function of the GABAAR. It does not induce P450 enzymes like the barbs do. It can produce tolerance and dependence.

SLIDE 36: Buspirone (Buspar) is a unique drug that is an anxiolytic and not a hypnotic. It is not related to barbs or benzodiazepines and indeed it doesn't act on GABAAR. Its actions are believed to be mediated through the 5-HT1A and DA 2 receptors. It doesn't produce tolerance and dependence so there are no withdraw symptoms associated with its discontinuation.

SLIDE 37: Ramelteon, ram el' tee on (Rozerem; 2005) is another rather unique drug that is a hypnotic. It is not related to barbs or benzodiazepines and indeed it doesn't act on GABAAR. It is an agonist of the melatonin MT1 receptor; activation of the melatonin receptor promotes the onset of sleep. Ramelteon is not a controlled substance, and it does not alter sleep patterns etc.In fact tolerance does not develop even after six months. Generally well tolerated, but side effects include nausea and vomiting, etc.

…SSRI's like paroxetine are often used off-label as anxiolytics

SLIDE 38: Suvorexant (Belsomra- Merck; 2014) is still another rather unique drug that is a hypnotic. It is a orexin receptor antagonist- with orexin receptors involved in sleep-wake cycle. Clinical studies indicate is reasonably effective, non habit forming, with most significant side-effect being next day somnolence- sometime severe. Hypnotic effect still in effect following 12 months of use- worth trying!

SLIDE 39: Meprobamate-rarely used, similar to barbs, site of action unknown.

Beta-blockers: propranolol most common; nadalol and atenolol less CNS side-effects.

SLIDE 40: I'll take two slides to mention skeletal muscle relaxants. As we discussed, benzodiazepines are good skeletal muscle relaxants that act at the GABAA receptor. Baclofen is a p-chlorophenyl GABA and it selectively acts at the GABAB receptor, which is also an inhibitory receptor in the CNS. However, GABAB receptors are not ion channels, they are G-protein receptors. They act to reduce NT release. They also act via second-messenger systems to stimulate K channel function, which hyperpolarizes the neuronal membrane. Their inhibitory actions in the spinal cord and brain are thought to underlie their antispasmatic actions. They are very useful for treatment of spinal injury and multiple sclerosis. They have no ant anxiety actions nor hypnotic actions, so they are not considered drugs of abuse.

SLIDE 41: Dantrolene is also used for reduction of spasticity in patients with paralysis or MS. It blocks the release of Ca from the SR in muscle cells. It is typically given to the nonambulatory patient because it can cause muscle weakness. It has relatively few side effects. However, in some cases it can cause liver dysfunction. It has another use in malignant hyperthermia, a condition which is triggered by certain general anesthetics or skeletal muscle blockers. Its reduction of Ca release decreases the skeletal muscle contractions and reduces temperature.

SLIDE 42: Study Guide

1) Know sedative/hypnotic's effects on stages of sleep and their interaction with the GABAAR.
2) Know advantages of benzodiazepines over barbiturates
3) Know that barbs enhance P450 metabolism and understand the consequences.

SLIDE 43:

4) Know the significance of half lives for benzodiazepines
5) Drug list (those drugs listed in lecture script and ppt): uses, metabolism, side effects, duration of action.

First Aid Basic Sciences Organ Systems, 2nd Edition: Chapters 6 and 7.