Hypnotics

Hypnotics are drugs that act as CNS depressants. Drugs of the first generation (barbiturate and non-barbiturate hypnotics) act primarily on the ascending part of the reticular formation, hypothalamus, thalamus and cerebral cortex. Hypnotics of second and third-generation effects mainly on the limbic system.

Hypnotics decrease vigility (vigilance). The effect is graduated according to the dose size in order **sedation-hypnosis-narcosis**.

Sedation means calming the patient (motorically and mentally). Sedatives are considered to be those drugs that do not lead in themselves to the induction of sleep. Those are for example plant extracts (Valerian Officinalis – *Tinctura valerianae*, Maypop – **Passiflora incarnata** – NOPASSIT®, also bromisoval, guaifenesin – sedative, anxiolytic, myorelaxant). Some drugs included in this group in larger doses can still induce sleep(bromisoval, phenobarbital). They are considered complementary drugs.

Hypnosis represents a condition similar to physiological sleep. The ideal hypnotic should maintain the physiological sequence of REM and nonREM phases. However, most drugs shorten REM sleep, leading to insufficient "sleep". After discontinuation of treatment a "rebound phenomenon" may occur, i.e predominance of REM sleep, which brings unpleasant dreams and repeated awakenings (i.e. results in waking up and subsequent insomnia).

Mechanism of action

All hypnotics act on the GABA-benzodiazepine macromolecular complex, which is related to the activity of the chloride channel in a biomembrane of a neuron. GABA (gamma-aminobutyric acid) is an inhibitory mediator that occupies its specific receptor, thereby leading to the opening of the channel and so the flow of chlorine ions intracellularly, so the intracellular potential decreases ever further. The consequence is hyperpolarization of the biomembrane and inhibition of the function of the neuron. The occupation and influence of the benzodiazepine (BZ) receptor near the GABA receptor enhances the inhibitory influence of the mediator itself – GABA.

Indication

- **sleep disorders**
- **sleeplessness (insomnia): inability to fall asleep, short sleep with early awakening, shallow sleep with frequent awakening.**

First-generation

At present, they are no longer in this indication for their non-specific effect, easy induction of drug dependence, high toxicity (respiratory centre depression) and numerous interactions with other drugs (induction of metabolism, especially barbiturates). This group includes mainly **barbiturate hypnotics**.

Second generation – benzodiazepine hypnotics

They are currently the drugs of choice in insomnia therapy. These hypnotics suppress REM sleep lightly or moderately strongly. Liver microsomal enzymes under their prolonged influence are not subject to induction. For these drugs, the range between toxic and therapeutic doses (i.e the pharmacotherapeutic window) is wide.

With repeated administration, the risk of drug dependence is lower than with barbiturates. Withdrawal syndrome occurs under the image of insomnia, tremor, in more severe cases as epileptic seizure, hallucinations and delirium. The severity of withdrawal symptoms depends on the last doses of hypnotics (the higher the dose, the more dangerous the manifestations of withdrawal syndrome), on the value of the biological half-life of the drug (the shorter the half-life, the greater the danger of provoking withdrawal syndrome).

Benzodiazepines have a *specific antagonist at the BZ receptors* – flumazenil. With its use, the effect of benzodiazepines (not barbiturates or alcohol) can be quickly abolished.

Benzodiazepines are synergists of all CNS depressant drugs. They have adverse effects on memory and other cognitive function (concentration of attention and judgement, learning ability), which can manifest as amnesia, a disorder of continuity of consciousness, especially in the elderly. Benzodiazepines are not suitable for people, where increased attention and reactivity are required (driving, operating machinery). They also enhance the effects of alcohol and invertedly alcohol inhibits the metabolism of long-acting benzodiazepines (e.g. inhibition is still evident 10 hours after the last dose of diazepam).

There is *cross-tolerance* between hypnotics and alcohol may be also included. This explains, why the effects of standard doses of hypnotics cannot be achieved with sufficient effect in individuals with a history of recent excessive use of these hypnotics or alcohol.

Drugs from both groups of anxiolytics pass rapidly through the placental barrier. They are metabolised slowly by the fetus. A teratogenic effect has not been proved but some authors describe a higher incidence of cleft lip and palate, lower birth weight and length of fetuses of mothers, which used these drugs in the first trimester of pregnancy. If given in the last trimester they may lead to toxic manifestations in the newborn(lethargy, hypotonia,

hypothermia - so-called "floppy infant") or a withdrawal syndrome (tremor, tachypnoea, convulsive manifestations, etc.). It is therefore recommended to discontinue anxiolytics as early as one month before delivery. Benzodiazepine anxiolytics pass into breast milk and may lead to excessive sedation of the infant. Therefore, mothers with a medium to long $t_{1/2}$should not breastfeed.

Benzodiazepines with strong hypnotic and weak anxiolytic effects

They also have a weak myorelaxant effect and their effect is therefore non-specific.

Short-acting (up to 6 hours after the last dose)

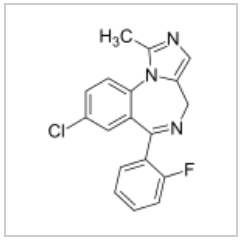
- **Midazolam** – Used as a premedication before short-term surgical or internal procedures - gastroscopy, colonoscopy.

Medium long-acting(8-10 hours)

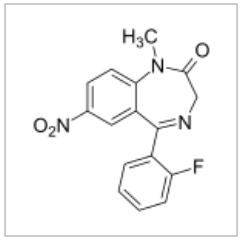
- **Flunitrazepam**.

Long-acting

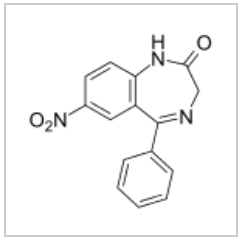
- **Nitrazepam, flurazepam** – characterised by residual morning effects (drowsiness) and the possibility of cumulation.



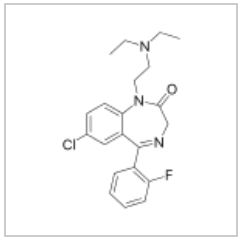
Midazolam



Flunitrazepam



Nitrazepam



flurazepam

Benzodiazepines with strong anxiolytic and weak hypnotic effect

- see Anxiolytics

The choice of medication is guided by the type of insomnia

1. for difficulty falling asleep, short-acting or medium long-acting hypnotics are used at usual doses, flunitrazepam at a low dose of up to 1 mg
2. for recurrent nocturnal awakenings, higher doses of short-acting or usual doses of medium-acting hypnotics are used
3. early waking without the need for morning vigilance is treated with long-acting hypnotics, if morning vigilance is needed medium-acting hypnotics may be used at the usual dose

It is a serious error to prescribe hypnotics for longer periods (usually more than 2-3 weeks).

Overview of side effects of non-specific hypnotics

- Residual [[somnolence and fatigue in the morning, especially due to drugs with a long biological half-life.
- danger of acculumation.
- Confusion(in the elderly).
- Stimulant effect instead of inhibition, exctitaion in children after barbiturates.
- Diazepam is associated with depression and suicidal attempts.
- Nightmares after Diazepam have also been described.
- Amnesia for the duration of the effect of the drug(i.e., anterograde amnesia, can be used for uncomfortable clinical examinations).
- "Rebound insomnia" after discontinuations of the drug.
- Potentiation of CNS depressant effect in combination with other agents.

Third generation

They do not shorten REM phase of sleep, they do not induce morning hangover or daytime sleepiness. They are not associated with memory impairment or rebound insomnia. Tolerance is not created, possibly not even drug dependence. Amnesia occurs only during the first two hours after administration. The following drugs have a moderate duration of action(5-7 hours):

zolpidem, zopiklon.

*Recently, however, it appears that addiction to third-generation drugs is occurring and they have side effects. Here are some case reports but in the Czech language: http://www.solen.sk/pdf/Pilch.pdf https://www.psychiatriepropraxi.cz/pdfs/psy/2009/05/10.pdf, http://www.cspsychiatr.cz/detail.php?stat=990

Other sleep-inducing drugs

They provide an opportunity to avoid using conventional hypnotics.

We can take advantage of the hypnosedative effects of **neuroleptics** - a small dosage of levomepromazine and chlorprothixene. If depression contributes to morning insomnia, dosulepin can be prescribed in a single dose at night. A similar approach can be taken if intense pain needs to be suppressed at the same time. Another option is to use hydroxyzine. For children, **promethazine** (H1 lytic) is suitable for sooting, e.g.during allergic episodes, itching etc.

Links

Related articles

- benzodiazepines
- beznzodiazepines(pediatrics)
- benzodiazepine intoxication
- psychopharmaticuals
  - sedatives
  - anxiolytics

External links

- Hypnotic (english wikipedia)

Used literature

- MARTÍNKOVÁ, Jiřina – MIČUDA, Stanislav – ČERMÁKOVÁ, Jolana. *Vybrané kapitoly z klinické farmakologie pro bakalářské studium : Hypnotika, sedativa* [online]. ©2001. [cit. 2010-07-01]. <https://www.lfhk.cuni.cz/farmakol/predn/bak/kapitoly/cns/hypnotika-bak.doc/>.
- RABOCH, Jiří – ZVOLSKÝ, Petr. *Psychiatrie.* první edition. Galén, 2001. 622 pp. pp. 413. ISBN 80-7262-140-8.