Benzodiazepines

Benzodiazepines (BZD, BDZ, BZs) are highly effective drugs with anxiolytic, sedative, anticonvulsant, muscle relaxant, hypnotic, and amnesic actions. They are among the most commonly prescribed classes of psychoactive drugs, primarily because of their fast and highly specific effect. However, they are also quite often **overprescribed and abused**.

5mg/ml Diazepam for intravenous use

Indications

- **Anxiety disorders and phobias, stress, mixed anxiety-depression disorders**;
- **acute agitation** - agression of various nature (e.g. mania, schiophrenia, somatics illness, etc.);
- **withdrawal symptoms and detoxification** in alcohol and barbiturate dependency;
- **sleeping disorders**, insomnia;
- **epilepsy**, status epilepticus;
- **akathisia**, muscle spasms, and spasticity
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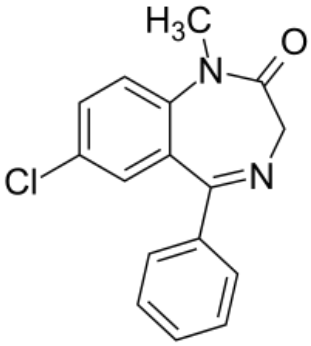
Contraindications

- **Oversensitivity to benzodiazepines**;
- **myasthenia gravis** (except tofisopam);
- **acute intoxication** by alcohol, hypnotics, psychoactive drugs, analgetics, and other substances with depressive effect on the CNS;
- **gravidity** and **lactation**,
- alcohol or substance **abuse**
- **sleep apnea**, sensory and cerebellar **ataxia**, severe **liver** or **kidney disease**, **chronic respiratory failure**



The skeletal structure of diazepam

Common adverse effects

- Daytime fatigue and somnolence, decreased alertness - increased risk of a traffic accident!;
- ataxia, confusion, dizziness, hypotension, risk of falling;
- respiratory insufficiency (particularly when combined with CNS depressants);
- paradoxical reactions, such as anger, irritability, aggression, euphoria, insomnia;
- amotivational syndrome - apathy and passivity.

Dependence and withdrawal

Long-term and regular use of high doses of benzodiazepines leads to increased tolerance and **dependence**. Since the therapy of BZD addiction is difficult and time-costly, prevention is the key in this regard. BZs should only be used when necessary and when no safer alternatives are available. The total period of usage should be limited to the shortest time possible (most commonly 4-6 weeks). Predispositions for benzodiazepine dependence are chronic somatic diseases (particularly chronic pains), personality disorders, alcohol or other addictions, and chronic sleep disorders.

Abrupt dose reduction or discontinuation may lead to **benzodiazepine withdrawal syndrome**, followed by *rebound phenomena* - anxiety, insomnia, agitation. The most common symptoms of the withdrawal are irritability, increased perspiration, nausea and emesis, tremor, headache, muscle tension, dysphoria, insomnia, dysphoria, insomnia, tension, and palpitation. Severe withdrawal symptoms include delirium, confusion, epilepsy seizures, psychotic states including hallucinations or paranoia. To prevent withdrawal syndrome, it is most important to decrease the BZD doses gradually over several weeks. If the withdrawal syndrome manifests, low doses of BZD are reintroduced to ease the symptoms. The use of antiepileptics (e. g. carbamazepine) is also recommended in such cases.

Overdose

Overdose clinically manifests by somnolence, slurred speech, muscle hypotonia, and respiratory depression with possible myocloni or coma followed by decreased blood pressure and low pulse. It is treated by the antagonist of benzodiazepine receptors - *flumazenil*.

List of commonly used benzodiazepines

- **Alprazolam (Xanax)** – has a highly specific anxiolytic effect, and is used for the treatment of anxiety disorders, panic disorders, and also for short-term therapy of neurotic-induced insomnia.

- **Diazepam (Valium)** – a sedative with a long-lasting effect, has strong anxiolytics effects but has also significant hypnotic, anticonvulsive, and muscle relaxative effects. Has a very fast onset of effects. Diazepam is used to treat agitation with psychomotor restlessness, anxiety, status epilepticus, and spasticity. Prolonged use may lead to dependence. Dosage differs among patients, ranging from 2 to 50 mg, with maximum doses being used before sleep.
- **Bromazepam** – has a similar effect as diazepam, also has an antidepressive effect. Used for pre-surgery sedation.
- **Clonazepam** – besides the anxiolytic use has an anticonvulsive effect and is indicated for spasticity and epilepsy (including absence seizures). It is also used to treat withdrawal symptoms of alcohol dependence. Compared to alprazolam and bromazepam, clonazepam has increased sedative and hypnotic effects.
- **Oxazepam** – has a shorter and weaker effect than diazepam but with fewer side effects, and is therefore often used in ambulatory care.

Side effects of alprazolam

- **Tofisopam** – has no muscle relaxant effect, and can be used in patients with myopathy - including myasthenia gravis.
- **Nitrazepam** – long-lasting and effective hypnotics used to prevent nocturnal or early awakening. Has muscle relaxant effect (suitable for insomnia caused by pain from increased muscle tonus), does not have active metabolites
- **Flunitrazepam** – hypnotic with medium-term effect used for troubles with falling asleep (mostly historically, is no longer used because of side effect and potential for abuse)

Benzodiazepines sorted by effects

Anxiolytics

Drugs with prevalent anxiolytic effects are used in this indication.

List of benzodiazepine anxiolytics by elimination half-life (t 0,5; brackets contain usual daily doses used for anxiolytic effect)

- **long $t_{1/2}$** (> 24 hours):
  - *diazepam* (5–40mg), *medazepam* (10–60 mg), *clobazam* (20–30 mg), *clonazepam* (0,5–4 mg), *chlordiazepoxide* (10–50 mg),
  - are biotransformed by oxidative reactions in the liver
  - their elimination is prolonged in patients with decreased liver function and elderly people
- **medium $t_{1/2}$** (12 – 24 hours)
  - *alprazolam* (0,5 – 4 mg) *bromazepam* (3 – 15 mg)
- **short $t_{1/2}$** (<12 hours):
  - *oxazepam* (30 – 90 mg), *tofisopam* (50 – 300 mg), *lorazepam* (2 – 6 mg)
  - are metabolized by conjugation with glucuronides with significantly lower dependence on liver function

Hypnotics

BZs represent contemporary **drugs of choice** in the therapy of insomnia. They belong to the second generation of hypnotics.

These hypnotics suppress the REM phase with light or moderate effect. Their long-term use does not cause an increase in hepatic microsomal enzymes. There is a significant difference between toxic and therapeutic doses.

The risk of dependence caused by prolonged use is lower than in barbiturates. Withdrawal syndrome manifests by insomnia, tremor, in more severe cases as an epileptic seizure, hallucinations, and delirium. Severeness of withdrawal symptoms depends on the latest doses of hypnotics (the higher the dose, the more severe are the symptoms of withdrawal syndrome), the biological half-life of the drug (the lower the half-life, the higher is the risk of causing withdrawal syndrome).

Benzodiazepines have *a specific antagonist on BZ receptors* - ***flumazenil***. Its use can quickly counter the effect of benzodiazepines (but not barbiturates nor alcohol).

Benzodiazepines are synergists of all drugs that cause the depression of the CNS. They have adverse effects on memory and other cognitive functions (concentration and judgment, learning capability), which may manifest as amnesia, the disruption of memory continuity, especially among elderly people. They are not well suited for people that require high alertness and fast reactions (driving, operating heavy machinery). They increase the effects of alcohol and inversely, the alcohol inhibits the metabolism of long-duration benzodiazepines (e.g. the inhibition lasts for 10 hours after taking the last dose of diazepine).

Hypnotics, including alcohol, are affected by *cross-tolerance.* This explains why it is impossible to cause sufficient effect in patients with a history of alcohol or hypnotics abuse.

Drugs of both categories of anxiolytics quickly pass through the placental barrier. The fetus doesn't metabolize them as quickly as an adult. The teratogenic effect hasn't been proved, but some sources describe the increased incidence of cleft lip and palate and low birth weight and length in feti of mothers that used these drugs in the 1st trimester of pregnancy. If they are used in the 3rd trimester, they may lead to toxic manifestations in the newborn (lethargy, hypotony, hypothermia - so-called "floppy infant") or withdrawal symptoms (tremor, tachypnoea, spasticity, etc.). It is therefore recommended to stop using anxiolytics one month before the childbirth. Benzodiazepine anxiolytics pass to the mother's milk and may lead to sedation of the infant. Because of this, mothers using anxiolytics with medium to long half-life shouldn't breastfeed.

1. Benzodiazepines with **strong hypnotic** and weak anxiolytic effects
    - They also cause muscle relaxation. Their effect is non-specific.
    1. Short-lasting effect (less than 6 hours after the last intake)
        - **Midazolam** - takes effect for less than 6 hours after the last intake. It is used in premedication for short surgical or internal procedures - gastroscopy, colonoscopy, stomach surgery.
    2. Středně dlouho působící (8–10 hod), Medium-lasting effect (8 - 10 hours)
        - **Flunitrazepam**
    3. Dlouhodobě působící Long-lasting effect,
        - **Nitrazepam, flurazepam -** have residual morning effects (drowsiness) and a possibility of dose cumulation.
2. Benzodiazepines with **strong anxiolytic** and weak hypnotic
    - see the *Anxiolytics* above.

Sedatives

Sedatives are substances that cause sedation, a decrease of psychic and motoric activity, drowsiness, and fatigue. They are used to sedate patients treated with hypertension, vegetative dystonia (increased perspiration, palpitation, hot flashes), and others. Their toxicity is low.

Antiepileptics (anticonvulsives)

BZD belongs to 2nd generation antiepileptics. Others in this category are clonazepam, diazepam, lorazepam (status epilepticus, absence seizure)

- status epilepticus requires i. v. diazepam, lorazepam, midazolam
- **mechanism of the effect of BZD antiepileptics**: *potentiation of GABA'S effect* (also valproate, barbiturate, vigabatrin, tiagabine)

Muscle relaxants

Benzodiazepines are acting as central muscle relaxants.

Muscle relaxants:

- Affect spasticity (myotonolytics)
- Suppress mono- and polysynaptic reflexes in the brain and spinal cord
- Takes effect in the GABA area, decreasing the generation of action potentials in the neurons

Benzodiazepines:

- Stimulate GABA's effect and open Cl channels
- Relax the muscles (muscle relaxant) and psyche (anxiolytic)

Another example of central muscle relaxants is baclofen.

Links

Related atricles

- Antiepileptics
- Anxiolytics
- Hypnotics

References

Used literature