Benzodiazepines (peditarics)

Benzodiazepines are **tranquilizers** and are not anesthetics in the proper sense of the word. Depending on the dose , **it has a sedative, anxiolytic, anticonvulsant and hypnotic effect** . In anesthesiology, they are used to potentiate the effect of anesthetics or for sedation during local anesthesia. In addition, benzodiazepines have an important role as **premedication agents**.

Pharmacological effects- general characteristics

The effect is dependent on the size of the dose → the higher the dose, the faster the effect starts, the longer the effect lasts and the more marked its intensity up to a certain ceiling (*ceiling effect*). Major common effects include:

- sedation
- anxiolysis
- hypnotic effect
- anticonvulsant efficacy
- muscle relaxation

Higher doses of benzodiazepines lead to **depression of vigilance up to a hypnotic effect** , but not analgesia .

The anxiolytic, muscle relaxant and anticonvulsant **effects of** benzodiazepines are **mediated by the GABA receptor** , the hypnotic effect occurs elsewhere. Prolonged administration of benzodiazepines, e.g. in intensive care, leads to CNS receptor deregulation with the subsequent **development of tolerance** to the effect of benzodiazepines.

The vast **majority of** benzodiazepines **can induce anterograde amnesia** , which varies in length for individual substances. The reliability of the onset of amnesia is > 85%. Nevertheless, amnesia is not certain in all cases, and it does not have to be balanced and of the same quality throughout the entire duration. Effects on the cardiovascular system are very small in cardiac healthy patients. The combination with an opioid increases the depressant effects on hemodynamics. After iv administration, benzodiazepines temporarily lead to a slight depression of breathing. Respiratory arrest rarely occurs after intravenous administration of any of the benzodiazepines.

Injection of water-insoluble benzodiazepines can lead to thrombophlebitis .

Biotransformation takes place in the liver . According to the elimination half-life, benzodiazepines can be divided into **short-acting** (midazolam), **medium-long-acting** (flunitrazepam) and **long-acting** (diazepam) substances.

Clinical use of benzodiazepines

Benzodiazepines are mainly indicated for the following purposes:

- premedication
- addition of substances such as opioids or ketamine
- sedation during regional/local anesthesia
- sedation, or hypnotic effect for short and painless performances
- introduction to anesthesia in high-risk patients
- anticonvulsant: midazolam, diazepam

The disadvantage of diazepam and flunitrazepam is **local pain upon injection** and the **risk of thrombosis** as well as the possibility of prolonged action. The listed side effects are significantly milder with midazolam.

Contraindications

Benzodiazepines cannot be used in conditions and situations:

- **myasthenia gravis**
- **hypersensitivity to benzodiazepines**

Diazepam

Diazepam (Apaurin, Seduxen, Valium) is a **long-acting** benzodiazepine. The acidic pH value is the reason why its iv and im administration is associated with **local pain** . An interesting fact is that all the company's diazepam preparations contain 10 mg of the active substance in 2 ml of solution.

Pharmacological effects [edit | edit source]

After iv administration of diazepam, **the sedative effect begins within 1-2 minutes** . The required dose is highly variable. **The combination** of benzodiazepines **with an opioid significantly increases the** sedative and hypnotic effect . In addition, adverse effects on breathing and the cardiovascular system are highlighted. Diazepam (as well as other benzodiazepines) is characterized by a new rise in plasma concentration 6-8 hours after iv or post-administration and may be associated with resumption of sedation and drowsiness. The rise in plasma concentration again is apparently a consequence of enterohepatic recirculation . Repeated administration leads to accumulation of diazepam and its metabolites in adipose tissue with subsequent prolongation of sleepiness.

Due to uncertain resorption and painful injection, the preparation should not be administered via the intravenous route. **IV administration** should be slow and the widest possible vein should be used for it, and it should also be **flushed with a bolus of physiological solution immediately after administration .**

Diazepam dosage [edit | edit source]

- **sedation** : 0.1–0.3 mg/kg iv, dosing interval approx. 8 hours
- **anticonvulsant effect** : 0.2–0.4 mg/kg iv, can be repeated 1–2 times up to a total dose of 1 mg/kg, single dose should not exceed 10 mg iv in children, alternatively possible pr administration in a dose of 0.5 mg/ kg (in principle, we give 5 mg pr. to children under 3 years old, 10 mg pr. to older people)

Flunitrazepam

Flunitrazepam (Rohypnol) a **medium-long** -acting benzodiazepine. The substance maintains stability in 5% glucose or in 1/1 FR for about 8 hours. The preparation Rohypnol contains 2 mg of the active substance in 1 ml of solution, to which 1 ml of solvent is added for dilution immediately before administration.

Pharmacological effects [edit | edit source]

The pharmacodynamics of flunitrazepam correspond to a large extent to diazepam, but its **sleep-inducing effect is stronger** . Amnesia is also more pronounced. After a slow iv injection, sleep occurs within 3 minutes, **the duration of sleep is about 20-30 minutes** , and then there is a longer time of sedation.

Flunitrazepam is **also given primarily to supplement TIVA** or combined IV anesthesia for long-term procedures. In intensive care, it is used as a **sedative and hypnotic** . **Per os** is also administered as **a premedication**. The product is unsuitable for ambulatory patients due to its long duration of action.

Flunitrazepam dosage [edit | edit source]

The dosage of flunitrazepam is 0.02–0.03 mg/kg IV

Midazolam

Midazolam (Dormicum, Midazolam) is a **short-acting** benzodiazepine. Its **injection is not painful**. The preparation Dormicum contains 5 mg in 1 ml of solution, ready for immediate administration. The solution in the ampoule is compatible with 5% glucose and with 1/1 FR, the prepared mixture is stable for 24 hours.

Pharmacological effects [edit | edit source]

The pharmacological effects of midazolam also largely correspond to those of diazepam, but midazolam has the following different properties compared to diazepam:

- 2x stronger efficiency
- shorter duration of effect
- solubility in water
- rapid and complete resorption after IM administration with a half-time of resorption of 10 minutes

The onset of the effect is usually 30–60 seconds , the duration of the effect 15–30 minutes . Midazolam is used **for premedication, to supplement TIVA** or combined intravenous anesthesia. After administration po, pr or im it is almost completely resorbed and its **effect starts quickly** . A significant prolongation of the effect of midazolam must be expected when repeating bolus injections and smaller doses. **Too fast administration, administration of too high a dose even leads to a temporary depression of breathing** . Rapid IV administration in hypovolemic patients causes transient systemic hypotension . The combination of midazolam with opioids leads to an additive or synergistic respiratory-depressant effect.

Midazolam dosage [edit | edit source]

- premedication: 0.05–0.1 mg/kg iv
- sedation: 0.1 mg/kg iv
- introduction to anesthesia: 0.2 mg/kg iv
- anticonvulsant effect: 0.2 mg/kg iv or im, ev. then continuously 0.05–0.3 mg/kg/hour. iv
- sedation of patients during UPV: 0.1–1 mg/kg/hour. iv
- rectal administration: 0.3–0.6 mg/kg per dose
- intranasal administration: 0.2–0.4 mg/kg, cave! – irritation in the nose, limited volume

Flumazenil

Flumazenil (Anexate) is a **specific benzodiazepine antagonist** that is used in clinical practice. The substance shows high specificity and affinity for benzodiazepine receptors. **Competitively** and directly dependent on the size of the dose, it displaces benzodiazepines from their binding to receptors.

Pharmacological effects [edit | edit source]

The plasma half-life of flumazenil is approximately 1 hour, the effect is also short. This can lead to re-sedation caused by the original agonists. Therefore, it must often **be given in repeated doses or continued after the initial dose by continuous infusion. Low doses of** flumazenil **have a stimulating effect , high doses have a depressant effect** . Flumazenil has no cardiovascular effects and no effect on breathing. Sedation, unconsciousness , respiratory depression, and psychomotor effects of benzodiazepines disappear within 1–3 minutes. **The duration of the effect of flumazenil depends on the dose** and on the specific properties of benzodiazepines.

Indication [edit | edit source]

The indication spectrum of flumazenil is narrow:

- therapeutic **antagonism of benzodiazepines**
- differential-diagnostic **administration in coma of unclear etiology**

Serious **adverse effects and contraindications** have not yet been recorded after flumazenil. The biggest "disadvantage" of flumazenil appears to be its **high price .** The therapeutic range is large. In theory (and in practice) flumazenil can cause a **superacute withdrawal syndrome**, especially in people addicted to benzodiazepines.

Flumazenil Dosage [edit | edit source]

The dose for flumazenil is 0.01 mg = 10 µg/kg.

Links

Related Articles

- Anesthesia (pediatrics)
- Intravenous anesthetics (pediatrics)
- Inhalation Anesthesia (Paediatrics)
- Neuroleptics (pediatrics)
- Opioids (pediatrics)

Source

- HAVRÁNEK, Jiří: *Pharmacology in intensive care* .