Opioids (pediatrics)

Opioids are among the most frequently used substances in anesthesiology and in postoperative pain therapy. We distinguish between **endogenous opioids** (enkephalins, endorphins, and dynorphins), **naturally occurring opioids** (components of opium juice), and **synthetic opioids** (fentanyl). The most important desired effect of opioids is **significant analgesia**. Other effects are **respiratory depression, sedation, elevated mood, reduced GIT motility, nausea, and vomiting** as well as **changes in vegetative and endocrine functions**. The effects of opioids are mediated by a reaction with **opioid receptors**, of which we recognize three main types: **μ, ƙ, δ** receptors.

For the purposes of intensive care and anesthesia, the following are mainly used: **fentanyl, remifentanil, alfentanil, and sufentanil**.

The most important **indications** for the use of opioids are:

- supplementing the effect of inhalation anesthetics;
- the analgesic component of TIVA;
- primary "anesthetic" in at-risk patients;
- postoperative pain therapy;
- premedication;
- analgosedation: e.g. patients on UPV.

The collective name opioids include all agonists and antagonists with a morphinomimetic effect of natural and synthetic origin.

Endogenous opioid peptides bind to opioid receptors, for which we currently distinguish 3 classes:

- **μ-receptors**: activation of μ-receptors causes analgesia (primarily supraspinal), euphoria, miosis, respiratory depression, cough suppression, and constipation;
- **c-receptors**: mediate analgesia at the spinal and supraspinal levels;
- **δ-receptors**: they mediate analgesia at the spinal and supraspinal levels.

All 3 types of receptors are not only found in the central nervous system, but also in the periphery.

Classification of opioids according to receptor action

The effect of opioids is produced by acting on one or more types of receptors in specific tissues. Ligands act as agonists and have high intrinsic activity, as partial agonists with little intrinsic activity, or as antagonists with no intrinsic activity. Accordingly, we can distinguish **4 groups of opioids**:

- **pure agonists**: morphine, pethidine, fentanyl, remifentanil, alfentanil, and sufentanil – are pure selective agonists on the μ-receptor, their analgesic effect is primarily caused by the activation of the μ-receptor, as well as respiratory depression, mitosis, reduced GIT motility and euphoria;
- **partial agonists**: buprenorphine – partially and selectively activates the μ-receptor, has a smaller maximum effect, but is 30 times stronger than morphine in terms of analgesics;
- **mixed agonist-antagonists**: nalbuphine, and pentazocine – they are partial agonists on the κ-receptor and antagonists on the μ-receptor, selective κ-agonists have an analgesic effect on the supraspinal level, but also dysphoric and psychomimetic (disorienting and depersonalizing);
- **antagonists**: naloxone is a pure selective antagonist at μ-receptors, but in very high doses it also binds to ƙ and δ-receptors.

Pharmacological effects - general characteristics

The desired dose of opioids, or plasma concentration, must always be determined individually. As the intensity of painful stimuli changes during surgery or invasive procedures, the consumption of opioids also changes accordingly.

For doctors, the most important **central and adverse effects** are:

- analgesia,
- drowsiness,
- the feeling of well-being or euphoria,
- respiratory depression,
- muscle stiffness,
- miosis (high doses lead pathognomonic to "pin" narrowing of the pupils),
- attenuation of the cough reflex,
- nausea and vomiting.

The effects of opioids are dose-dependent. Therapeutic doses lead to pain relief or analgesia and drowsiness. There is a decrease in the secretion of saliva, sometimes there is itching in the face.

Analgesia

The pain-relieving or pain-relieving effect of opioids is highly selective. Other senses, such as touch, vibration, sight, and hearing, are not affected. Constant, dull pain is better relieved than sharp, intermittent pain (eg, colic). With a high dosage, we can completely suppress practically any pain, but with the simultaneous occurrence of respiratory depression or apnea. The **analgesic effect** of opioids occurs at the spinal level and at numerous supraspinal sites in the CNS, probably also at peripheral opioid receptors. Opioids, even in very high doses, **do not reliably induce unconsciousness** and must therefore be combined with i.v. anesthetics or sedatives - hypnotics. Additionally, **opioids do not induce amnesia**.

Respiratory depression

All opioids already lead to respiratory depression in analgesic doses, probably o**n the basis of a direct depressant effect on the respiratory centers** in the medulla oblongata. Opioid-induced respiratory depression is dose-dependent and is potentiated by lack of stimulation or sleep or concomitant i.v. anesthetic and sedative. **Death from opioid overdose** is almost exclusively caused by **central respiratory depression**.

Clinically, respiratory depression is manifested, always depending on the size of the dose, in the following way: decrease in respiratory rate initially with increased tidal volume → decrease in respiratory rate with a decrease in tidal volume → severe bradypnea → apnea.

Opioid premedication increases arterial pCO2 by about 5–10 mmHg. However, even this hypercapnia is dangerous in patients with intracranial hypertension, lung disease, or an unstable cardiovascular system.

Opioids suppress the cough reflex, thereby increasing the risk of bronchial obstruction, atelectasis, and hypoxemia. In some patients, inducing vomiting while suppressing the coughing mechanism further increases the risk of pulmonary aspiration.

Muscle rigidity

Opioids can increase muscle tone to the point of muscle rigidity. T**he muscles of the chest, abdomen, and larynx are mainly affected**. Rigidity usually begins within 60–90 seconds after i.v. injection of an opioid or with the onset of unconsciousness. At maximally expressed muscle rigidity, apnea occurs at the same time, so UPV is needed.

High doses or rapid injection facilitate the development of muscle rigidity, on the other hand, prior induction of anesthesia with an intravenous anesthetic or inhalation anesthetic prevents this.

Abnormal flexion movements of individual muscle groups up to **tonic-clonic movements** of numerous limb muscles, which resemble generalized convulsive seizures, can also be induced by the effect of opioids.

Neuroexcitatory manifestations

Opioids can cause excitatory manifestations, which can manifest as **nystagmus, flexion of individual limbs, or tonic-clonic activity** of trunk and limb muscles. **Fentanyl** can in very rare cases lead to **delirium** and **grand-mal activity**, as can sufentanil.

Nausea and vomiting

Nausea and vomiting are **typical side effects of opioids and other μ-receptor agonists**. They are not dependent on the route of administration or the type of opioid. Opioid-induced nausea can be reduced by the administration of droperidol or phenothiazine.

Tolerance and addiction

The continuous supply of opioids over a longer period of time **leads to the development of tolerance**, or to addiction to CNS effects: the duration of the effect is shortened, and the analgesic, sedative, euphoric and respiratory depressant effects are weakened. The rate and extent of tolerance development appear to be proportional to the dose. However, there are differences between individual opioids. **Highly potent opioids** such as fentanyl or sufentanil **develop less tolerance** than less potent opioids such as morphine. Tolerance can be broken by increasing the dose of the opioid. **Discontinuing the opioid for a longer period of time will prevent the development of tolerance.**

In addition to tolerance, chronic opioid intake also leads to addiction. **Abrupt discontinuation of opioids** after prolonged administration leads to **withdrawal syndrome**.

Cardiovascular effects

Due to their v**ery small adverse cardiovascular effects**, opioids are among the most commonly used drugs in cardiovascular risk patients.

Opioids lower blood pressure, mainly by arterial vasodilatation and a decrease in venous return. Hypotension can be corrected by elevating the limbs, and volume therapy, however, during long-term treatment with opioids, support with vasoconstrictors is often necessary. Opioids **decrease heart rate**. Significant bradycardia, which

requires treatment, develops not infrequently after intravenous administration, especially of alfentanil or remifentanil. Bradycardia may be further enhanced when propofol is administered at the same time. **Opioid-induced bradycardia can be reversed by the administration of atropine.**

Effects on the gastrointestinal system

Opioids stimulate circular smooth muscle of the GIT and urogenital tract while **suppressing propulsive activity by rhythmic contractions of longitudinal muscle**. Spasms and constipation can result.

Opioids **decrease gastric acid production and decrease gastric motility**. Opioids **decrease bile and pancreatic secretions and delay the digestion of food in the small intestine**. In the bile ducts, opioids increase the pressure, thereby **preventing the emptying of bile into the small intestine**. In the urogenital tract, through induced detrusorsphincteric dyssynergia, they lead to **urine retention**.

Other effects

Opioids in **the skin area lead to vasodilation**. Morphine and semi-synthetic opioids such as pethidine and some analogs can r**elease histamine from basophils**. **Histamine release** is probably dose-dependent and **results in vasodilation with a fall in blood pressure**. It may be affected by prior administration of a combination of H1 and H2 blockers, but not by naloxone. A**nother typical side effect of opioids is itching**.

Interaction with other drugs

Hypnotics

Combination of opioids with hypnotics, or i.v. anesthetics usually lead to a reduced dosage of both groups of drugs to **induce unconsciousness**. With the respiratory depressant and cardiovascular effect of opioids, we can expect a synergistic effect when combined with hypnotics. **Respiratory depression is enhanced**, as is the hypotensive effect and, in the case of propofol, also often the bradycardic effect.

Inhalation anesthetics

All μ-agonists reduce the minimum alveolar concentration of the inhaled anesthetic. Conversely, inhaled anesthetics potentiate the central effects of opioids, including synergism in respiratory depression. The effects of the combination on autonomic, endocrine, and cardiovascular functions are complex, as numerous factors, such as spontaneous breathing or UPV, and the presence or absence of painful stimuli, play an important role.

Neuroleptics

We call the combination of opioids with a neuroleptic (droperidol) **neuroleptanalgesia = a state of analgesia and neurolepsy with preserved consciousness**. The combination of both groups of drugs **leads to hypotension and weakening of sympathetic reflex responses** to sympathetic stimuli, while respiratory depression is primarily conditioned by the opioid alone. Tracheal intubation is not a standard procedure for neuroleptanalgesia.

Balanced anesthesia

This currently **most commonly used procedure of intubation anesthesia** has several pharmacological components:

- strong opioid: fentanyl, alfentanil, sufentanil, remifentanil;
- inhalation anesthetic: nitrous oxide or isoflurane, sevoflurane;
- non-depolarizing muscle relaxants.

A significant advantage of balanced anesthesia compared to pure inhalation anesthesia is **better surgical analgesia**, with a reduced dosage and with fewer cardiovascular effects.

Fentanyl

Fentanyl **binds to the μ-receptor** similarly to morphine but has a 50-100x stronger effect.

Pharmacological properties

Fentanyl is **very lipophilic** and **quickly penetrates the blood-brain barrier**. After a low-dose bolus injection of 1-3 μg/kg, the duration of action of fentanyl is usually less than 1 hour. At a high dose (> 20 μg/kg), plasma concentrations do not fall into the subtherapeutic range during the distribution phase and fentanyl becomes a long-acting agent. Repeated bolus injection also leads to a prolonged effect. However, **high doses** lead to **significant muscle rigidity**, which negatively affects or even prevents adequate ventilation.

Indications and dosage of fentanyl

Most often, fentanyl is used t**o supplement inhalation anesthetics**, further as an **analgesic component of TIVA**, as a supplement for i.v. anesthetics for the induction of anesthesia or for t**he analgosedation of patients on UPV**.

Dosage:

- 1–3 μg/kg i.v. as a bolus in patients without UPV, 5–10 ug/kg i.v. as a bolus in patients on UPV;
- analgosedation of patients on UPV: continuous dose 4–10 ug/kg/hour;
- suppression of response to intubation: 1–5 ug/kg i.v. before injecting the hypnotic.

Alfentanyl

The strength of its effect corresponds to about a quarter of the analgesic potency of fentanyl, but **the duration of the effect is shorter.**

Pharmacological properties

The effect of alfentanil **starts very quickly and lasts only a short time**. The maximum analgesic and respiratory depressant effect occur in less than 2 minutes, the duration of the effect i.v. the bolus in a low dose is often only 15 minutes or even shorter, with higher doses we must expect a prolongation of the effect. The pharmacodynamic effects of alfentanil correspond essentially to those of fentanyl. The substance **can lead to significant bradycardia**, which can be further enhanced by the simultaneous administration of propofol. **Blood pressure can drop significantly**, especially with rapid injection and in combination with intravenous hypnotics. Respiratory depression after alfentanil lasts less than after fentanyl.

Indications and dosage of alfentanil

Due to its short effect, alfentanil is mainly **used for shorter procedures** (less than 15 minutes long), but also as **an analgesic component of TIVA**. However, in this direction, the use of remifentanil is more advantageous.

Dosage:

- initial bolus for short procedures: 3–5–10–(15) ug/kg i.v., with repeated administration of 1/3–1/2 of the initial dose;
- before intubation initially, 30-50 ug/kg over 5 minutes.

Sufentanil

Sufentanil has **7-10 times stronger analgesic effect than fentanyl**. Is item no. the strongest analgesic used in clinical practice. **The onset of action is faster** than that of fentanyl and **lasts less time**.

Pharmacological properties

The pharmacodynamic spectrum corresponds to fentanyl, alfentanil and remifentanil. In principle, after the administration of higher doses, we must expect several hours of respiratory depression and significant analgesia in the postoperative phase.

Sufentanil is **a highly selective μ-receptor agonist** with corresponding pharmacodynamic effects of this group. **Higher doses** (1–2 ug/kg) often result in marked **muscle rigidity and myoclonic jerks**.

Indications and dosage of sufentanil

Sufentanil is mostly used as **a supplement to balanced anesthesia**, it is also **suitable for analgosedation of patients on UPV**. The administration of sufentanil **should be reserved for patients with airway management**.

Dosage:

- bolus dose: 0.3–0.5–(1) ug/kg IV;
- before intubation: 0.3-1 ug/kg i.v. about 1-3 minutes before intubation;
- analgosedation of patients on UPV: continuous dose 0.5–2–3 ug/kg/hour. i.v.

Remifentanil

Remifentanil is (like fentanyl, alfentanil or sufentanil) i.v. an opioid with **a purely agonistic effect on the μ-opioid receptor and less binding to the ƙ, ω, δ receptors.** The effect sets in quickly and only lasts a very short time.

Pharmacological properties

Degradation of remifentanil **takes place continuously in the blood and tissues** by non-specific plasma and tissue **esterases**, **and thus independently of the activity of the kidneys and liver**. The elimination of remifentanil is independent of the duration of infusion in contrast to all other opioids. This corresponds to the fact that we can quickly adapt the dosage of remifentanil to different requirements. Even after a very long infusion, all μ-receptor mediated effects, including respiratory depression, are terminated as quickly as after short-term administration.

At more than 30% excess weight, central clearance is reduced for remifentanil. If we dose remifentanil according to the actual body weight, we must expect a prolongation of the effect. Therefore, in these patients, **the dosage should be chosen according to the ideal body weight**.

The analgesic effect of remifentanil is equivalent to that of fentanyl, while sufentanil is approximately 6-10 times more effective. Like all μ-agonists, remifentanil also **reduces the MAC value of commonly used inhalation anesthetics**. Remifentanil **causes**, like other μ-agonists, **respiratory depression up to apnoea** in a dose-dependent manner. It is worth noting that the sedative and respiratory depressant effects are so close to each other that already sedating doses (0.06-2 ug/kg/min) can induce respiratory depression. But even after the use of very high doses - in contrast to other opioids - there is only a very small risk of respiratory depression in the postoperative phase when the patient has regained consciousness and spontaneous breathing has resumed.

Remifentanil, like other μ-agonists, **can increase muscle tone to the point of muscle stiffness**. **A drop in blood pressure and bradycardia** are typical cardiovascular side effects of remifentanil.

TIVA

Total intravenous anesthesia (TIVA) is defined as **a technique of general anesthesia in which** - as opposed to combined anesthesia - **we use exclusively i.v. a drug with the aim of inducing unconsciousness, analgesia, amnesia, muscle relaxation, and achieving control of sympathoadrenergic reactions.**

In terms of pharmacological properties, **the combination of remifentanil and propofol is most suitable for TIVA**.

Practical procedure:

- Premedication with atropine 0.02 mg/kg (preferably IM) to prevent bradycardia or asystole during laryngoscopy in case of vagus irritation.
- Initiation of remifentanil infusion at individually adjusted dosage, e.g. 0.1–0.25–0.5 ug/kg/min. and infusion of propofol at a rate of 5–6 mg/kg/hour. To shorten the induction phase, anesthesia can be induced with a bolus of propofol immediately after the onset of remifentanil action.
- After intubation: reduce remifentanil rate to about 0.1 ug/kg/min. and propofol rates to 2–4 mg/kg/hr.
- Until painful stimulus (skin incision, cannulation, puncture): increase remifentanil infusion rate to 0.2 ug/kg/min. or more - as needed.
- In the phases of intensive surgical stimulation, increase the infusion rate of remifentanil to 0.5 ug/kg/min or even more.

Because **remifentanil does not accumulate** and its effect can be quickly terminated, we can maintain the infusion of remifentanil until the end of the operation or a few minutes before its end. On the other hand, t**he disadvantage of the very rapid termination of the effect of remifentanil is the occurrence of pain in the early phase after a painful procedure** => initiation of analgesic therapy shortly before the end of the operation (central and/or non-steroidal analgesics may be used).

Naloxone

We can antagonize the effect of opioids with **specific antagonists**, which are **derivatives of opium**. Naloxone is most commonly used clinically to antagonize the effect of opioids.

Naloxone is a pure opiate antagonist without an agonistic effect, i.e. it does not act like an opioid or enhance the effects of opioids. The substance has a competitive antagonistic effect on all opioid receptors but has the highest affinity for μ-receptors. The blockade is reversible and can be reversed by subsequent agonist injection.

Indications and dosage

Naloxone is **indicated in conditions with an excess of opioids**, e.g. in the postoperative period with respiratory depression and limitation of consciousness, or as a differential diagnosis **in comatose states of unclear etiology**. Naloxone **may induce withdrawal syndrome in opioid-dependent patients**.

Dosage:

- repeated **i.v.** or bursts of 0.1 mg/kg, up to a maximum of 2 mg for dosage! – in this case, first intubate and UPV → ensure normocapnia (if the condition does not improve after the 2nd-3rd dose, another cause must be sought).

Naloxone can be given i.v. or i.m. After i.v. injection, opioid-induced respiratory depression is antagonized within 1–2 minutes, as is the analgesic and sedative effect. Often unresponsive patients wake up in a flash. **After higher shock doses**, **blood pressure and heart rate may rise significantly**, and **heart rhythm disturbances or**

pulmonary edema may occur. **Titration dosing is therefore more appropriate**. **The duration of the effect** usually **does not exceed 45-60 minutes**. If we administered high doses of opioids, we must expect a possible return of respiratory depression after this period. Therefore, adequate **cardiopulmonary monitoring** of these patients for a sufficiently long period of time is desirable.

Links

Related articles

- Anesthesia (pediatrics)
- Intravenous anesthetics (pediatrics)
- Inhalation Anesthesia (Paediatrics)
- Neuroleptics (pediatrics)
- Benzodiazepines (pediatrics)
- Morphine
- Equianalgesic doses of opioids
- Opioid analgesics

Source

- HAVRÁNEK, Jiří: *Farmakologie v intenzivní péči*.