Naloxone

Introduction

Naloxone is a medication used to counteract, reverse or block the effects of opioids, especially in the case of an overdose.

But what are opioids? For that, one has to also understand what opiates are and how those two differ:

- **Opiates** are naturally occurring Alkaloids that derive from the opium poppy. Natural and synthetic substances, which work like morphine and bind on opioid receptors, are described under the term “opioids”

**Naloxone is an opioid**

**Opioids**, which are, as apparent, the subject of interest, are distinguished based on certain criteria to:

**Endogene and exogene opioids (depending on their relation to the organism):**

- Endogene opioids appear naturally in the organism and regulate the conditions of the stress reaction.
- Exogene opioids are administrated to the body from the outside and do not exist naturally.

**Naloxone is an exogene opioid**

**Opioid –Agonists and –Antagonists**

- Opioid –Agonists bind on the opioid receptor of the nerve-cells, something which stimulates them.
- Antagonists usually work in such a way that they take the agonists’ place, therefore antagonizing for the same kind of binding.

**Naloxone is an opioid-antagonist**

**Action of opioid-agonists**

Opioid Agonists work extremely extensive and varyingly. They can alleviate pain, reduce the function of the central nervous system and bring about a sentiment of euphoria. They also affect attention and sufficient breathing, trigger obstipation and can make someone addicted.

It is therefore made clear, what the importance and usage of opioid-antagonists is.
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In order for the functions of opioid agonists' and antagonists' to be better understood, one should also, shortly, describe how the **opioid receptors** function:

**Opioid Receptors:**

Opioid Receptors are situated in the **brain**, the **spinal cord** and the **peripheral nervous system**. The opioid receptors consist of the: $\mu_1, \mu_2, \delta, \kappa, \epsilon$ and ORL. These are coupled with **GTP-binding proteins**.

*Naloxone can bind on every opioid receptor, but its highest binding affinity lies with the $\mu$ receptors which are followed by the $\delta$ and $\kappa$ ones.*

(It is therefore made clear that should an agonization on those receptors arise, the antagonization through the usage of Naloxone is in any case possible)

- The $\mu_1$-Receptor has a reduced effect on cAMP, consequently on the calcium influx and the therefore on the associated transmitter release. These receptors are located on the spinal cord and the brain and work analgesic (soothing), but also towards undercooling, euphoria and pupil contraction.
- The $\mu_2$-Receptor is located on the spinal cord as well as on the peripheral nervous system and favors the opening of the potassium canals, something which leads to hyperpolarization. Furthermore when there is an elevated partial pressure of CO$_2$ then the receptor doesn’t react so well, which in turn can lead to breathe depression. The propulsive motor activity is likewise mitigated, thus disturbing digestion.
- The $\kappa$-Receptor lies on the spinal cord and brain and can trigger pain relief, breathe depression and dampening of the function of the central nervous system.
- The $\delta$-Receptor lies on the brain, the spinal cord and the peripheral nervous system and can work analgesic.

**Structure and Synthesis**

**Structure:**
- one benzene ring, two cyclohexane rings, one THF ring and one piperidine ring
- two hydroxy groups
- one ether linkage
- one tertiary amine
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Antagonist on Opioid-Receptor

Does not bind on Opioid-Receptor

Can antagonize on a Receptor, who takes part in a non-specific immunoreaction

**Synthesis:**

To synthesize naloxone from oxymorphone, the tertiary amine needs to be demethylated and alkylated with an Allyl group. The phenol is protected as an acetate and the compound is then converted to its N-oxide. Treatment with the Burgess reagent yields oxazolidines. As of now, it is not known how the oxazolidine is created. It is assumed that sulfonation by the Burgess reagent occurs at the N-oxide, which either leads to the hydroxy group trapping the iminium ion into forming a ring or displacing the triethylammonium salt. The former idea would represent a 5–endo–trig closure.

The ketone is protected as a ketal. After that, the amine is alkylated through a Grignard reaction and the phenol and ketone are de-protected.
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**Overdose**

Naloxone, as an antagonist, binds on the μ, δ and κ receptors of the nerve cells and therefore *reverses or inhibits the opioid’s effect*. Its rapid effect makes it ideal as a lifesaving drug to be used in emergencies in order to avoid death by overdose. But how does Naloxone actually saves a life? When overdosing, the heartbeat slows and so does the breathing rhythm. Naloxone works in such a way that it increases those two, while at the same time antagonizing other opioids, thus saving a life. In that sense, one could also rely on the usage of adrenaline or noradrenalin. The latter two have unfortunately other side effects, and do not antagonize opioids either, and could very well be proved fatal if administrated. Precisely because Naloxone works in that particular way, raising the heartbeat and increasing the breathing rhythm, one must really be careful when administrating this particular drug on people that suffer from a heart disease or who are also being administrated opioid-based painkillers. Naloxone has to be administrated intramuscularly, and therefore has to be injected through the gluteal muscles, thighs or arms. Naloxone that is injected comes in a lower concentration (0.4mg/1mL) than Naloxone that is sprayed up the nose (2mg/2mL).

**The side effects of pure-Naloxone usage include:**

- Tempering of thoughts and distortion of reactions (non-permanent)
- Nausea
- Diarrhea
- Dizziness
- Light-headedness
- Fever
- Shivering
- Increased blood pressure
- Increased heartbeat
- Nervousness
- Accumulation of fluids in lungs
- Hyperventilation
- Sweating

Naloxone is nonetheless non-addictive. Naloxone does not have an analgesic or a painkilling function, since, through binding on the opioid receptor, it can’t cause any conformational changes and could therefore be called a pure opioid-antagonist. The binding affinity is mainly directed towards the μ-Receptors, but also in a minor form on the δ- and κ- Receptors. In comparison to every other Opioid that may have been used, Naloxone possesses a higher binding affinity (with the only exception being buprenorphine). Through competitive inhibition it is made possible for Naloxone (even in small doses) to supplant
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opioids like morphine, as a ligand on the receptors, thus leading to their inactivation. Naloxone takes effect up to 8-10 times faster than morphine in the central nervous system, with its effects starting 10-20 minutes after the inter-nerve or intramuscular administration, whereas its half-life is about 20 to 70 minutes (usually $t_{1/2} = 30\text{min}$). Its effects fade after approximately 90 minutes from the administration.

**Clinical usage**
A titrated dosage of Naloxone is primarily used to avert a respiratory depression and sedation. Through the titration a pain exacerbation (sudden increase of pain) can be prevented, since Naloxone can competitively hinder endorphins produced from the body, which regulate the sense of pain. An opioid like morphine has a longer half-life (2-3 hours) than Naloxone, and should therefore be noted that, after a certain amount of time, the effects of morphine could return thus a potential need of re-administration of Naloxone rises anew. A further titrated dosage of Naloxone is crucial in order to prevent withdrawal symptoms, should the patient at hand be one with a chronic opioid medication administration or opioid addiction.

**Pain relief:**

**Principle:**
Through the usage of opioids as analgesics, there are often (gastro-intestinal) side-effects. Naloxone may not be an analgesic, but can, through its function as an antagonist of opioid-induced obstipation, counteract such effects. Should an analgesically acting opioid be combined with Naloxone, then a painkiller with a much smaller gastro-intestinal risk is created.

**Usage: degenerative spinal column disease:**
During a study about a degenerative spinal column disease, scientists used an Oxycodone/Naloxone preparation on patients suffering from acute pain, caused by such a disease, to measure the pain-intensity, intestine-function and quality of life. In each of those parameters there was a noticeable improvement. Below is a table which presents their results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity:</td>
<td>From 5,5 to 3,0</td>
<td>10-Point Scale</td>
</tr>
<tr>
<td>Bowel function:</td>
<td>From 38,6 to 14,8</td>
<td>100-Point Scale</td>
</tr>
<tr>
<td>Quality of life:</td>
<td>From 40,6 to 23,8</td>
<td>70-Point Scale</td>
</tr>
</tbody>
</table>
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Naloxone combinations:

**Oxycodone/Naloxone:**

Oxycodone is used as a painkiller, whose analgesic effects appear after the drug enters the liver-passage, since there, amongst others, the enzymatic decomposition of Oxymorphone happens, which is a rather effective analgesic. Obstipation is, for long-term patients, a problematic side effect of the opioid pain-relief therapy (so even with Oxycodone), since the opioids at the peripheral receptors bind with the gastrointestinal track. Because of that binding on the $\mu_2$ receptor, increased amounts of acetylcholine are secreted and the propulsive motor activity is therefore disturbed. That is also the main cause for opioid-induced obstipation. Naloxone has a high first-pass-effect; it is firstly decomposed in the liver and had, for that reason, no high bioavailability through oral administration. It does however still competitively inhibit the opioid-agonists at the gastric-receptor and could therefore prove a remedy for obstipation.

Such an example of Oxycodone/Naloxone-Preparation is Targin®

**Tilidin/Naloxone:**

Tilidin is also a painkiller, which shows its analgesic effects after passing through the liver passage.

The Tilidin/Naloxone-Preparation should be administrated orally.

In case of an abusive, intravenous administration, Naloxone works competitively against Tilidin.

**Buprenorphine/Naloxone:**

Buprenorphine can be administrated through the oral mucosa as an opioid substitute during an opioid withdrawal. This way, Naloxone cannot pass into the interior of the cell.

In case of an abusive, intravenous/nasal administration, Naloxone acts inhibitly and would therefore cause withdrawal symptoms.

**Side effects by the usage of the Oxycodone/Naloxone-Preparation:**

Like every other kind of medicine, it's also possible for this one to have specific side effects, which may not necessarily appear to everyone.

The most important ones, for which one should watch out are:

Breathing depression; the most dangerous risk of an opioid-overdose. Appears most
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commonly on elderly or weakened patients. For those particular patients there is also the chance of a serious drop in their blood pressure, due to the opioids. The side effects of the Oxycodone/Naloxone preparation have been categorized in four cases, depending on their frequency of appearance, and concern patients that were treated due to pain:

**Common (may affect up to 1 in 10 patients treated):**

<table>
<thead>
<tr>
<th>Common Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomachache</td>
<td>Constipation</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Indigestion</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Nausea</td>
<td>Bloating</td>
</tr>
<tr>
<td>Decrease in appetite to appetite loss</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Headache</td>
<td>Heat flushing</td>
</tr>
<tr>
<td>Weakness</td>
<td>Tiredness or fatigue</td>
</tr>
<tr>
<td>Itching</td>
<td>Skin reactions / rash</td>
</tr>
<tr>
<td>Sweat</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Sleepiness</td>
</tr>
</tbody>
</table>

**Uncommon (may affect up to 1 in 100 patients treated):**

<table>
<thead>
<tr>
<th>Uncommon Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thought disorders</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Depressions</td>
<td>Confusion</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Biliary</td>
<td>Withdrawal symptoms</td>
</tr>
<tr>
<td>Malaise</td>
<td>Pain</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Pain</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Runny nose</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>Cough</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Increased urinary urgency</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td></td>
</tr>
<tr>
<td>Muscle twitching</td>
<td></td>
</tr>
<tr>
<td>Muscle aches</td>
<td></td>
</tr>
</tbody>
</table>
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Rare (may affect up to 1 in 1,000 patients treated):
- Acceleration of the pulse
- Changes in the teeth
- Yawning
- Weight gain

Not known (from the available data cannot be estimated):
- Euphoric mood
- Erectile Dysfunction
- Hallucinations
- Flattening and slowing of the breathing (respiratory depression)
- Severe drowsiness
- Nightmares
- Belching
- Tingling in hands and feet
- inability to pass urine (urinary retention)

Abolition of a morphine-induced obstipation through the oral administration and usage of Naloxone

Background:
The most common side effect of a chronic-pain therapy with opioids is obstipation. Such a side effect is caused mostly due to the binding of an opioid on the receptors of the gastrointestinal track and could be repressed through the oral administration of Naloxone, without the analgesic effect being abolished due to the high, presystemic elimination of Naloxone.

Protocol:
In a therapeutic trial 15 patients, which had been treated for chronic pain with morphine and were therefore obstipated, were treated by oral administration of Naloxone. Results: 12 of the patients already had a strong bowel movement in one to four hours after the first administration (1:1 dosage-relation to morphine) of Naloxone, whereas three of the patients still showed no bowel movement even after a repeated Naloxone administration. The Naloxone dosage was reduced after the first day on a 2%-15% of the morphine-dosage for those patients. The analgesia was reduced by 10%-15% through oral administration of oral Naloxone. Even after the increase of the morphine-dosage, the obstipation did not return.
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