Naloxone

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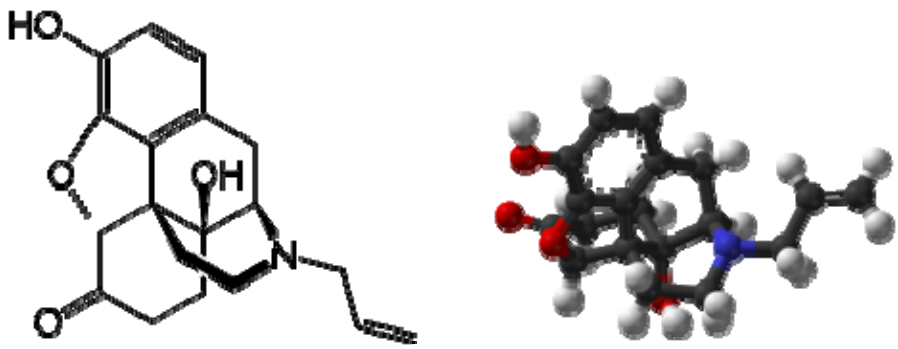

Naloxone

Naloxone, sold under the brandname **Narcan** among others, is a medication used to reverse the effects of opioids, especially in overdose.[2] Naloxone may be combined within the same pill as an opioid to decrease the risk of misuse. When given intravenously, it works within two minutes, and when injected into a muscle, it works within five minutes.[2] The medication may also be used in the nose.[3] The effects of naloxone last about half an hour to an hour.[4] Multiple doses may be required, as the duration of action of most opioids is greater than that of naloxone.[2]

Administration to opioid-dependent individuals may cause symptoms of opioid withdrawal, including restlessness, agitation, nausea, vomiting, a fast heart rate and sweating. To prevent this, small doses every few minutes can be given until the desired effect is reached. In those with previous heart disease, further heart problems have occurred.[2] It appears to be safe in pregnancy, after having been given to a limited number of women.[5] Naloxone is a pure opioid antagonist. It works by reversing the depression of the central nervous system and respiratory system caused by opioids.[2]

Naloxone was patented in 1961 by Jack Fishman, Mozes J. Lewenstein, and the company Sankyo. The drug was approved for opioid overdose by Food and Drug Administration in 1971.[6] Naloxone is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[7] Naloxone is available as a generic medication and is not very expensive.[2][8] Its wholesale price is between 0.50 and 5.30 USD per dose.[9]

Medical Uses

Opiate overdose

Naloxone is useful both in acute opioid overdose and in reducing respiratory or mental depression due to opioids.[2]

It is included as a part of emergency overdose response kits distributed to heroin and other opioid drug users, and this has been shown to reduce rates of deaths due to overdose.[10] A prescription for naloxone is recommended if a person is on a high dose of opioid (>100 mg of morphine equivalence/day), is prescribed any dose of opioid accompanied by a benzodiazepine, or is suspected or known to use opioids nonmedically.[11] Prescribing naloxone should be accompanied by standard education that includes preventing, identifying, and responding to an overdose; rescue breathing; and calling emergency services.[12]

Preventing opioid abuse

Naloxone may be combined with a number of opioids, including buprenorphine and pentazocine, so that when taken orally just the opioid has an effect; but if misused by injecting or taken in large doses, the naloxone blocks the effect of the opioid.[2][13] This combination is used in an effort to prevent abuse.[13]

Other

In a meta-analysis of people with shock, including septic, cardiogenic, hemorrhagic, or spinal shock, those who received naloxone had improved blood flow. The importance of this is unclear.[14]

Naloxone is also experimentally used in the treatment for congenital insensitivity to pain with anhidrosis, an extremely rare disorder (one in 125 million) that renders one unable to feel pain or differentiate temperatures.[*citation needed*]

Naloxone can also be used as an antidote in overdose of clonidine, a medication that lowers blood pressure.[15]

Side effects

Naloxone has little to no effect if opioids are not present. In people with opioids on board, it may cause increased sweating, nausea, restlessness, trembling, vomiting, flushing, headache, and has in rare cases been associated with heart rhythm changes, seizures, and pulmonary edema.[16][17]

Naloxone has been shown to block the action of pain-lowering endorphins which the body produces naturally. These endorphins likely operate on the same opioid receptors that naloxone blocks. Naloxone is capable of blocking a placebo pain-lowering response, both in clinical and experimental pain, if the placebo is administered together with a hidden or blind injection of naloxone.[18] Other studies have found that placebo alone can activate the body's μ-opioid endorphin system, delivering pain relief via the same receptor mechanism as morphine.[*citation needed*]

Special populations

Pregnancy and breast feeding

Naloxone is pregnancy category B or C in the United States.[2] Studies in rodents given a daily maximum dose of 10 mg naloxone showed no harmful effects to the fetus, although human studies are lacking and the drug does cross the placenta, which may lead to the precipitation of withdrawal in the fetus. In this setting, further research is needed before safety can be assured, so naloxone should only be used during pregnancy if it is a medical necessity.[19]

It is currently unknown if naloxone is excreted in breast milk.

Kidney and liver dysfunction

Currently, no established clinical trials have been conducted in patients with insufficient kidney function or liver disease, and as such, these patients should be monitored closely if naloxone is clinically indicated.

Pharmacodynamics

Naloxone has an extremely high affinity for μ-opioid receptors in the central nervous system (CNS). Naloxone is a μ-opioid receptor (MOR) competitive antagonist, and its rapid blockade of those receptors often produces rapid onset of withdrawal symptoms. Naloxone also has an antagonist action, though with a lower affinity, at κ- (KOR) and δ-opioid receptors (DOR). Unlike other opioid receptor antagonists, naloxone is essentially a pure antagonist with no agonist properties. If administered in the absence of concomitant opioid use, no functional pharmacological activity occurs (except the inability for the body to combat pain naturally). In contrast to direct opiate agonists, which elicit opiate withdrawal symptoms when discontinued in opiate-tolerant patients, no evidence indicates the development of tolerance or dependence on naloxone. The mechanism of action is not completely understood, but studies suggest it functions to produce withdrawal symptoms by competing for opiate receptor sites within the CNS (a competitive antagonist, not a direct agonist), thereby preventing the action of both endogenous and xenobiotic opiates on these receptors without directly producing any effects itself.[20]

The K_i affinity values of (−)-naloxone for the MOR, KOR, and DOR have been reported as 0.559 nM, 4.91 nM, and 36.5 nM, respectively, whereas for (+)-naloxone, 3,550 nM, 8,950 nM, and 122,000 nM, respectively, have been reported.[21] As such, (−)-naloxone appears to be the active isomer.[21] Moreover, these data suggest that naloxone binds to the MOR with approximately 9-fold greater affinity relative to the KOR and around 60-fold greater affinity relative to the DOR.[21]

Pharmacokinetics

When administered parenterally (non-orally or non-rectally, e.g. intravenously or by injection), as is most common, naloxone has a rapid distribution throughout the body. The mean serum half life has been shown to range from 30 to 81 minutes, shorter than the average half life of some opiates, necessitating repeat dosing if opioid receptors must be stopped from triggering for an extended period. Naloxone is primarily metabolized by the liver. Its major metabolite is naloxone-3-glucuronide, which is excreted in the urine.[20]

Administration

Naloxone is most commonly injected intravenously for fastest action, which usually causes the drug to act within a minute, and lasts up to 45 minutes. It can also be administered via intramuscular, subcutaneous injection or nasal spray.[22] There is a pre packaged nasal spray that does not require assembly and delivers a consistent dose. It can be repeated if necessary.[23] An non-FDA approved wedge device (nasal atomizer) attached to a syringe may be used to create a mist that delivers the drug to the nasal mucosa.[24] It is more common outside of clinical facilities where the majority of overdoses occur.[25][26]

The individual is closely monitored for signs of improvement in respiratory function and mental status. If minimal or no response is observed within 2–3 minutes, dosing may be repeated every 2 minutes until the maximum dose of 10 mg has been reached. If there is no response at this time, alternative diagnosis and treatment should be pursued. If person do show a response, they should remain under close monitoring, as the effects of naloxone may wear off before those of the opioids and the person may require repeat dosing at a later time.

Naloxone can be used orally along with Oxycontin Controlled Release and helps in reducing the constipation associated with opioids. Enteral administration of naloxone blocks opioid action at the intestinal receptor level, but has low systemic bioavailability due to marked hepatic first pass metabolism.[27]

In April 2014, the US Food and Drug Administration (FDA) approved Evzio, a hand-held automatic injector naloxone product that is pocket-sized and can be used in non-medical settings such as in the home. It is designed for use by laypersons, including family members and caregivers of opioid users at-risk for an opioid emergency, such as an overdose.[28] The approval process was fast-tracked as one initiative to reduce the death toll caused by opiate overdoses. At the time of approval, an estimated 16,000 annual deaths were attributed to prescription opioid overdoses in the US.[29]

Society and culture

Names

The patent for naloxone has expired. It is available in generic medication. Trade names include: Narcan, Nalone, Evzio, Prenoxad Injection, Narcanti, Narcotan, and others.

Legal status

In the US, naloxone is classified as a prescription medication, though it is not a controlled substance.[30] While it is legal to prescribe naloxone in every state, dispensing the drug by medical professionals (including physicians or other licensed prescribers) at the point of service is subject to rules that vary by jurisdiction.

While paramedics have carried naloxone for decades, law enforcement officers in many states throughout the country carry naloxone to reverse the effects of heroin overdoses when reaching the location prior to paramedics. As of July 12, 2015, law enforcement departments in 28 states carry naloxone to quickly respond to opioid overdoses.[31]

In Australia, as of February 1, 2016, naloxone is now available "over the counter" in pharmacies without a prescription.[32] It comes in single use filled syringe similar to law enforcement kits.

Prehospital access

Laws in many states have been changed in recent years to allow wider distribution of naloxone.[33][34] Several states have also moved to permit pharmacies to dispense the medication without the person first seeing a physician or other non-pharmacist professional.[35] Over 200 naloxone distribution programs utilize licensed prescribers to distribute the drug, often through the use of standing medication orders [36][37] whereby the medication is distributed under the medical authority of a physician or other prescriber (such as a pharmacist under California's AB1535).

Following the use of the nasal spray device by police officers on Staten Island in New York, an additional 20,000 police officers will begin carrying naloxone in mid-2014. The state's Office of the Attorney General will provide US$1.2 million to supply nearly 20,000 kits. Police Commissioner William Bratton said: "Naloxone gives individuals a second chance to get help".[38]

A survey of US naloxone prescription programs in 2010 revealed that 21 out of 48 programs reported challenges in obtaining naloxone in the months leading up to the survey, due mainly to either cost increases that outstripped allocated funding or the

suppliers' inability to fill orders.[39] The approximate cost of a 1 ml ampoule of naloxone in the US is estimated to be significantly higher than in most Western countries.[36]

Projects of this type are under way in many North American cities.[39][40][41] CDC estimates that the US programs for drug users and their caregivers prescribing take-home doses of naloxone and training on its use have prevented 10,000 opioid overdose deaths.[39] Healthcare institution-based naloxone prescription programs have also helped reduce rates of opioid overdose in North Carolina, and have been replicated in the US military.[36][42] Programs training police and fire personnel in opioid overdose response using naloxone have also shown promise in the US, and effort is increasing to integrate opioid fatality prevention in the overall response to the overdose crisis.[43][44][45][46][47] Pilot projects were also started in Scotland in 2006. Also in the UK, in December 2008, the Welsh Assembly government announced its intention to establish demonstration sites for take-home naloxone.[48]

Identification

Naloxone is the INN, BAN, USAN for the medication.

The CAS number of naloxone is 465-65-6; the anhydrous hydrochloride salt has CAS 357-08-4 and the hydrochloride salt with 2 molecules of water, hydrochloride dihydrate, has CAS 51481-60-8.

Media

The 2013 documentary film *Reach for Me: Fighting to End the American Drug Overdose Epidemic* interviews people involved in naloxone programs aiming to make naloxone available to opioid users and people with chronic pain.[49]