THERAPEUTIC DRUG MANAGEMENT AND TOXICOLOGY DIVISION NEWS

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In This Issue:

Naloxone: a Universal Antidote for Opioid Overdoses

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In the 1990s, pharmaceutical companies reassured the U.S. medical community that patients would not become addicted to new synthetic opioid pain relievers. With this reassurance, healthcare providers began to prescribe them at greater rates. This led to the misuse of these medications before it was known they could, in fact, become highly addictive. To compound this issue, cheap illicit fentanyl has recently become available and often been used as a cutting agent. As a result, the opioid overdose rate increased, and a staggering 46,802 Americans died in 2018. To combat this drug epidemic, naloxone has become much more accessible to the American public. Over the past decades it has gained a well-deserved reputation as the safest antidote to rapidly reverse an opioid overdose. In this article, we will discuss naloxone's general history, pharmacology, toxicity, laboratory testing, and current U.S. policies on its distribution and sale.

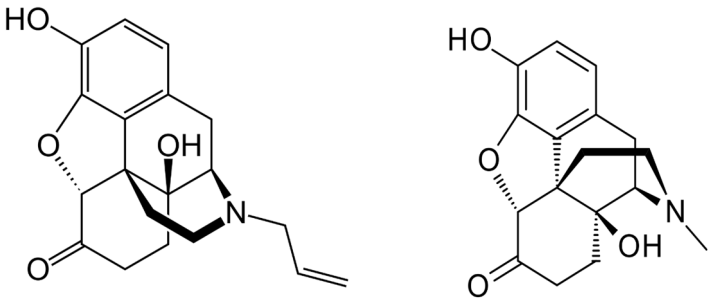
Background: Naloxone was first synthesized by Jack Fishman and Mozes Lewenstein in 1961 to develop a new treatment for opioid induced constipation. They quickly recognized its rapid ability to block opioid receptors in the central nervous system and that it had almost no analgesic properties. In 1971, the U.S. Food and Drug Administration (FDA) approved naloxone for treating opioid overdoses by intravenous (IV) or intramuscular (IM) injection. Once

administered, the overdosed person quickly begins breathing and regains consciousness. The Center for Disease Control and Prevention reported that from 1996 thru 2014, more than 26,000 opioid overdoses were reversed by non-medical personnel.

As the use of opioids has increased medical professionals began to experiment with new methods to administer naloxone quickly and safely under non-clinical conditions. In 2015, the FDA approved a nasal spray version, branded as Narcan, as a life-saving measure to try to stem the U.S. opioid epidemic. Naloxone is now often colloquially referred to as Narcan. This product requires no formal training and is easily used by the public. The federal governments push to expand naloxone's public use has led to its availability without a prescription in 43 states (1-2). The drug is stocked in hospitals and carried by emergency medical staff as well as law enforcement. In 2019, some U.S. universities began requiring all health science majors and resident advisors to be trained on its proper delivery.

Pharmacology: Naloxone, $C_{19}H_{21}NO_4$, is an opioid receptor antagonist primarily indicated for the treatment of opioid overdose, specifically to reverse respiratory depression. Commonly treated drug exposures include heroin, fentanyl, carfentanil, hydrocodone, oxycodone, and methadone. Naloxone is synthetically derived from oxymorphone; their structures are shown on Figure 1. The drugs differ in that the methyl group on the nitrogen atom is replaced by an allyl group in naloxone. Naloxone weakly binds to various plasma proteins, especially albumin, and it has a pKa of 7.9 (3). It has an estimated volume of distribution from 2.6 – 2.8 L/kg and has been shown to effectively penetrate the blood brain barrier and placenta. Its half-life has been reported to be 30-80 min and it is not listed as a controlled substance (3). There is no evidence of naloxone administration causing any tolerance or physical dependence.

Figure 1. Chemical Structures of Naloxone (left) and Oxymorphone (right).



The standard adult dose is 0.4 mg by IV or 4 mg by intranasal (IN) route of administration. Oral bioavailability is estimated to be only 2%, IN bioavailability is 4% and IM is 35% (3). The drug rapidly takes effect with the time dependent upon the route of administration. When given by IV an effect usually occurs in less than two min, by IM from 2 – 5 min and by an intranasal (IN) route in about five min. After administration, the person often spontaneously begins breathing and regains consciousness immediately. The duration of felt effects depends upon the route and dosage of naloxone administered and usually last from 30 – 60 min. Multiple doses are often required to treat overdoses as its duration of action is usually significantly shorter than most abused opioid drugs. If a response is not observed within 2 – 3 min, dosing should be repeated until a maximum dose of 10 mg is given. During this time, the person should be kept under continued surveillance to ensure they do not relapse. If at 10 mg no effect is observed one should consider another diagnosis.

The precise mechanism of naloxone's action is not fully understood. It appears to act as a competitive antagonist at the mu, kappa, and sigma opioid receptors in the central nervous system. It has the highest affinity with the mu receptor and can rapidly displace other opioids that are bound to it. Naloxone is metabolized in the liver by N-dealkylation into nornaloxone and reduction of the 6-keto group into naloxol both of which are usually glucuronidated (3-4). The primary urinary metabolite is naloxone-3-glucoronide. After oral or IV administrations from 60 – 70% is excreted in a 72 hr urine, with 25 - 40% appearing within 6 hr (5).

Naloxone is sometimes combined with another opioid to substantially decrease the risk of abuse of the latter. The primary example of this are suboxone pills which contain buprenorphine and naloxone in a 4:1 ratio. When ingested orally, the naloxone is poorly absorbed, and the buprenorphine will have the desired effect. However, if the tablet is solubilized and injected then the naloxone will greatly decrease the effects of buprenorphine.

Toxicity: Naloxone is considered a very safe medication. Alone it exerts little to no pharmacologic effect (2). In 2015, the American Association of Poison Control Centers reported no fatalities were due to it (6). At the standard doses of up to 1 mg/kg by IV, it had no effect in patients naïve to opioids or not dependent on opioids. As the IV dose increased to over 2 mg/kg,

patients have reported limited symptoms like dizziness, diaphoresis, yawning, nausea, and decreased cognitive performance (6).

The greatest toxicity concern is that naloxone can precipitate a severe withdrawal syndrome when given to those who are opioid-dependent or acutely intoxicated with opioids. Common symptoms include agitation, emesis, hypertension, and tachycardia. However, abrupt post-operative reversal of opioid depression may cause pulmonary edema or ventricular fibrillation in patients with pre-existing cardiovascular disease (5, 7). Recent American Heart Association guidelines recommend using the lowest effective dose to minimize this (5-6).

Laboratory Testing: Naloxone is routinely tested for in random urines at many commercial and university reference labs using liquid chromatography tandem mass spectrometry (LC-MS/MS). Some labs also test blood**.** Common confirmation cut offs are set at 2 ng/mL and many LC-MS/MS methods have been published (8). Naloxone is stable in plasma for 24 hr at room temperature and for 1.3 years at -20˚C (8).

At present, a selective immunoassay screen test is not available. Toxicologists should know that naloxone may cross-react with some opiate and oxycodone immunoassays and cause false positive results when at high concentrations. This was recently documented in a patient being prescribed suboxone who unexpectedly screened positive for oxycodone (9). A LC-MS/MS confirmation analysis revealed buprenorphine and naloxone above 1,000 ng/mL and the metabolite norbuprenorphine below 50 ng/mL. This strongly suggested adulteration with the patient likely crushing their prescribed suboxone and adding it into their urine sample.

Distribution and Sale: Greater awareness of the U.S. opioid epidemic has led to a range of public health and medical interventions, including widespread availability and use of naloxone to rescue overdose victims. Most states currently allow easy to administer naloxone to be sold over the counter to increase layperson access. Some states have passed Good Samaritan laws designed to provide legal immunity for liabilities to those who prescribe or dispense naloxone to include nonmedical bystanders (10). The Naloxone Prescriptions by Emergency Physicians Policy states physicians may prescribe naloxone to at-risk patients who have been discharged after an opioid intoxication, take high doses of opioids for pain management, are in mandatory

opioid detoxification or abstinence programs, or were recently released from incarceration and are a past opioid abuser (10).

With the increased public demand, the cost of naloxone has greatly increased in the U.S. despite generic forms of it being sold. This is especially true for the two products that were recently developed for use by the public; the nasal spray Narcan and the auto-injector branded as Evzio. Recently reported pricing for a dose of Narcan is ~$70 and Evzio is ~$2,000 (11). Meanwhile, a dose of the generic medication costs around $20. Most health insurance plans cover naloxone but finding a pharmacy that carries it can be difficult. A 2019 study found that it was more likely to be stocked in chain stores than in independent stores (1).

Conclusion, Despite its accidental discovery, naloxone has become a critical drug in today's opioid consuming society. Its ability to rapidly treat overdoses has made it essential for medical and emergency personnel to have access to it. Due to the opioid epidemic in America, naloxone has become readily available to the public as an over the counter drug which has saved countless lives. In an effort to protect those trying to help someone who has overdosed, Good Samaritan laws have been established to protect citizens trying to help the overdosed.

References.

1. Guadamuz JS, Alexander GC, Chaudhri T, Trotzky-Sirr R, and Qato DM (June 2019) Availability and Cost of Naloxone Nasal Spray at Pharmacies. from https://www.ncbi.nlm.nih.gov/pubmed/31173125. Accessed April 2020.
2. Jordan MR, Morrisonponce D (2020). Naloxone. In: Stat Pearls. Treasure Island, FL: Stat Pearls Publishing: https://www.ncbi.nlm.nih.gov/books/NBK441910/. Accessed April 2020.
3. Baselt R (2017). Disposition of Toxic Drugs and Chemicals in Man. 11th Ed. Seal Beach, CA: Biomedical Publications. pp 1488-89.
4. National Center for Biotechnology Information. PubChem Database. NALOXONE, Source =HSDB, https://pubchem.ncbi.nlm.nih.gov/source/hsdb/3279. Accessed April 2020.
5. Narcan nasal spray package insert. Accessed May 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208411lbl.pdf
6. Rzasa Lynn R and Galinkin JL (2018) Naloxone Dosage for Opioid Reversal: Current Evidence and Clinical Implications. *Therapeutic Advances in Drug Safety*, 9(1): 63–88.
7. McEvoy GK (2015) *AHFS Drug Information,* 1st Ed. Bethesda, MD: American Society of Health-System Pharmacists. pp 2182-85.

8. Fang WB, Chang Y, McCance-Katz, EF, and Moody, DE (2009). Determination of Naloxone and Nornaloxone by High-Performance Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry. *Journal of Analytical Toxicology*, 33: 409–17.
9. Gall B and El-Khoury JM (2019). Unusual Drug Test Results for a Patient on Buprenorphine and Naloxone. *Clinical Chemistry,* 65(10): 1332-33.
10. Expanding Access to Naloxone: A Review of Distribution Strategies (2019). https://ldi.upenn.edu/brief/expanding-access-naloxone-review-distribution-strategies. Accessed April 2020.
11. Is Naloxone Sold Over the Counter? (2020) https://health.clevelandclinic.org/is-naloxone-narcan-sold-over-the-counter/. Accessed May 2020.

Chair's Corner: Division News

It has been a very unusual year for most of us and the activities of the AACC Therapeutic Drug Monitoring and Toxicology Division have been unusually uneventful. With the 2020 AACC Annual Scientific Meeting being virtual this year in December, we will have no division activities during the meeting. Also, the division leadership decided not to award a Therapeutic Drug Monitoring and Toxicology Division Young Investigator Award this year but will call for and review nominations to name an awardee at the 2021 ASM. All division related abstracts that were submitted for the 2020 ASM were reviewed by the division leadership. Our Therapeutic Drug Monitoring and Toxicology Division Best Abstract Award winner for 2020, is Dr. Ruben (Yiqi) Luo, a post-doctoral fellow at the University of California San Francisco, for his abstract titled, "Exploration of Applying High-Resolution MS^2/MS^3 Mass Spectrometry for Screening Toxic Natural Products". Please be sure to check-out his abstract during the virtual meeting. Also, don't miss out on the excellent TDM/Tox content at the ASM which includes 11 roundtables and 13 scientific sessions. To review these and mark your calendars, visit the AACC ASM website and select to "search all conference sessions". Once on the search page, you can select the advance search options and type in the keywords "therapeutic drug monitoring" or "toxicology".

This is the time of year when we typically call for nominations to open positions in the division leadership. Recently, a Division Governance working group, composed of four current and past

division chairs, spent several months reviewing division governance processes. Based on their recommendation there will be changes to division officer terms and a shift of the division election cycle from calendar year to August 1 – July 31. AACC will be contacting each division to discuss these governance changes in greater depth and to assist with transitioning divisions to the new procedures. The goal is for the new processes and standardization to provide more efficient division operations, cohesion amongst divisions, and better alignment with AACC governance processes. More updates to come as we learn more on these important changes.

Kara Lynch

AACC TDM TOX Web Resources:

https://www.aacc.org/community/divisions/tdm-and-toxicology/

Upcoming Conferences/Courses

AACC National Meeting	Dec 13 to 17	Virtual Meeting

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AACC TDM TOX Division Leadership

Announcements:

The editorial board invites ideas and article contributions for this newsletter. Please contact Dr. Pradip Datta at pradip.datta@siemens.com.