HISTORICAL NOTES

Naloxone: sixty years of an essential antidote in emergency and prehospital care

Naloxona: 60 años de un antídoto esencial en los servicios de urgencias y emergencias

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Antidotes are drugs characterized by their ability to prevent, reverse, or neutralize the effects of a toxic agent. Although many medications could be included under this definition, few strictly meet these criteria, and one of them is naloxone.[1]

Sixty years have now passed since the introduction of this antidote into clinical practice, and we considered it of interest to review the historical aspects related to naloxone and its impact on the quality of care of patients with opioid and opiate overdose treated in emergency and prehospital services.

Opiates at the dawn of humanity

Homo sapiens living thousands of years ago in certain regions of Asia with temperate climates, clay-rich soils, and moderate altitude likely observed a herbaceous plant no taller than 150 cm, with simple leaves, pedunculated flowers, and a characteristic smooth capsule-shaped fruit containing black seeds. Although early human contact with this plant may have been as a potential food source, curiosity likely led to the observation of a sticky, milky-looking juice exuding from incisions made in the capsule. Through personal experience, this substance was found to possess hypnotic and analgesic properties, leading to the naming of the plant as the poppy and the latex as opium. Pliny the Elder, a Roman naturalist and philosopher, referred to the poppy as *Papaver* in the first century BC, although it was not until 1753 that the Swedish botanist Carl Linnaeus classified it as *Papaver somniferum.*

Sumerian tablets dated to 3000 BC and the Ebers Papyrus (1500 BC) already described the analgesic and sedative effects of opium. The Greeks and Romans used it to relieve pain, fatigue, and suffering, following the recommendations of Dioscorides and Galen. Arab physicians were highly knowledgeable about the use of opium, particularly for its antidiarrheal properties. Thomas Sydenham (1624–1689), the English physician renowned for describing acute childhood chorea, stated in 1680: "Among the remedies which Almighty God has been pleased to grant to man to relieve his sufferings, none is so universal and so efficacious as opium."

For centuries, opium was used as an analgesic medication, alone or mixed with ethanol (laudanum), as well as in rituals and ceremonies, leading to a growing number of addicted individuals and a flourishing trade surrounding the substance.

The identification of morphine in opium and its subsequent synthesis

In 1804, the German pharmacist Friedrich Sertürner succeeded in isolating morphine as the principal active substance in opium, naming it after Morpheus, the Greek god of dreams and visions. Morphine was thus the first alkaloid identified in dried poppy latex, ushering in a new era of pharmacology by transforming opium from a mixture of uncertain quantitative composition into a pure compound with safer and more effective therapeutic applications. However, it would take more than a century—until 1952—for Gates and Tschudi to synthesize morphine.[2] By then, the number of addicts and deaths from morphine overdose in Europe and the United States was steadily increasing.

At that time, no effective antidote existed to antagonize the effects of opiates. Mithridate, theriac, and other mixtures of plant and mineral products with presumed antidotal effects—used since Greco-Roman times—offered no benefit in opiate overdose. The early 20th-century use of analeptics such as picrotoxin proved largely ineffective.

The emergence of semisynthetic opioids

In the search for new analgesics with greater potency and lower addictive potential, Charles Wright acetylated morphine in 1874, synthesizing heroin. Although initially lacking clinical application, heroin was

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marketed in 1898 as an analgesic and antitussive purportedly less addictive than morphine—a claim quickly proven false. During the first half of the 20th century, other semisynthetic opioids with clinical applications were developed, including hydromorphone, oxycodone, and dihydrocodeine. Among these, heroin undoubtedly became the most prominent due to the extent of its use and its devastating effects.

The heroin epidemic reached global proportions after World War II, particularly in the United States and Europe from the 1970s onward. Injected heroin use was associated with severe medical complications, including fatal overdoses from respiratory depression, infectious diseases linked to needle sharing, and psychiatric and social disorders.

The consequences were devastating, with hundreds of thousands of deaths and a health and social impact that likely affected millions worldwide. In many countries, including Spain, heroin became the leading cause of drug-related death during the final decades of the 20th century.[3]

Introduction of nalodeine and nalorphine

At the beginning of the 20th century, what is considered the first specific antagonist of opioid receptors—specifically the μ receptor—was discovered: nalodeine, which was shown to block the effects of morphine. Although it was never marketed for human use, it paved the way for the development of new antagonists.

In 1915, nalorphine was synthesized and introduced into clinical practice during the 1940s and 1950s.[4] Although widely used until the 1960s, its partial agonist activity prevented complete reversal of overdoses; nevertheless, it represented a substantial improvement over previous therapies.

The arrival of naloxone

Naloxone is a pure opioid antagonist derived from thebaine, developed in 1961 by Blumberg, Lowenstein, and Fishman. The first human studies date back to 1963,[5,6] and its clinical approval as an opioid antagonist occurred in 1971, marking a milestone in the treatment of opioid overdose due to its favorable and decisive public health impact. Since then, naloxone has become the treatment of choice for heroin and other opioid overdoses, owing to its ability to rapidly and effectively reverse respiratory depression and restore consciousness. Initially used in hospital settings, its use quickly expanded to prehospital care.[7]

Currently, the World Health Organization continues to list naloxone as an essential antidote in its Model List of Essential Medicines. Current clinical toxicology guidelines recommend that naloxone be readily available for immediate use in emergency departments, both hospital-based[8] and prehospital.[9]

Naloxone's impact has been profound, resulting in an indisputable reduction in acute overdose mortality and preventing countless deaths and sequelae among heroin and opioid users. It is the most frequently used antidote in drug abuse intoxications in Spanish emergency departments.[10]

Naloxone in 2025: Indications, dosage in adults and children, and administration considerations

Naloxone is a pure opioid receptor antagonist with the following affinity order: $\mu > \delta > \kappa$. It antagonizes the effects of opiates and opioids, including analgesia, respiratory depression, miosis, coma, and hypotension. Naloxone is commercially available in 1-mL ampules containing 0.4 mg/mL. It is indicated in confirmed or suspected opioid intoxication when the patient is comatose (Glasgow Coma Scale score < 12) and has respiratory depression.

In the initial management of coma of unknown origin, empirical administration of naloxone constitutes a highly valuable diagnostic and therapeutic intervention, as it can rapidly reverse opioid-induced central nervous system depression, improving clinical status and guiding diagnosis ex *juvantibus*. For this reason, naloxone has long been included in the so-called "coma cocktail."[11] Naloxone is not indicated in conscious, agitated, or convulsing patients.

Naloxone is administered via direct IV injection. In adults, the dose ranges from 0.04 to 0.4 mg depending on clinical circumstances. If no response is observed, 0.2–0.4 mg boluses may be repeated every 2–3 minutes until respiratory improvement or a maximum dose of 4 mg is reached. Higher doses may be required in overdoses involving highly potent opioids such as fentanyl, but the total dose should not exceed 10 mg. In overdoses involving long-acting opioids, sedation may recur. In such cases, an additional bolus (0.2 mg) is recommended, followed by continuous infusion of 5% dextrose containing two-thirds of the dose required to normalize respiratory function per hour, adjusted according to clinical response. In all cases, improving ventilation is more important than restoring full consciousness.[12] In patients with opioid overdose who present with cardiac arrest, naloxone has not been shown to contribute to reversal of the arrest.

In pediatric patients, a recent study on prehospital naloxone administration showed that the antidote worsened the clinical condition in only 0.2% of cases, as the vast majority of children are not opioid users and therefore are not at risk of developing withdrawal syndrome.[13] In children on chronic opioid therapy, in adolescents with suspected long-term use, or in neonates born to opioid-dependent mothers, naloxone should be initiated at a dose of 0.01 mg/kg (maximum 0.4 mg) intravenously. In all other cases, higher doses may be administered (0.1 mg/kg, maximum 2 mg). If there is

no response, doses should be repeated every 2–3 minutes up to a maximum of 10 mg. If continuous infusion is required because of resedation, the same recommendations as in adult patients should be followed.

Furthermore, naloxone may be administered subcutaneously or intramuscularly and, exceptionally, via the intranasal or endotracheal route if IV access is delayed. More recently, an intranasal naloxone formulation has been marketed in several countries—though not in Spain—which in some settings does not require a prescription. This formulation may be particularly useful in environments or communities where opioids are used recreationally, allowing peers, family members, or friends to administer the antidote immediately if overdose is suspected. In these situations, a systematic review indicates that 2 mg intranasally is the most commonly used initial dose for successful overdose reversal.[14] However, according to the summary of product characteristics approved by the European Medicines Agency, a dose of 1.8 mg sprayed into one nostril is recommended for adults and adolescents aged 14 years or older, with repetition after 2–3 minutes if there is no response or if respiratory depression recurs.

Naloxone may precipitate an opioid withdrawal syndrome in dependent patients. Agitation is the most frequent sign, followed by diaphoresis, mydriasis, piloerection, and sinus tachycardia. Vomiting and seizures may also occur, potentially leading to aspiration and respiratory distress. Pulmonary edema associated with naloxone use has been described less frequently; however, it should be noted that many opioids, such as heroin, can themselves trigger noncardiogenic pulmonary edema with respiratory distress, making it difficult to establish causality.

The epidemic of synthetic opioid use

The most recent major drug epidemic involves synthetic opioids, with fentanyl playing a central role. In 1960, Paul Janssen synthesized fentanyl, a compound with potency far exceeding that of morphine, inaugurating a family of analogues (sufentanil, alfentanil, remifentanil, among others) that revolutionized anesthesia and acute pain management. In parallel, compounds with different pharmacodynamic profiles were developed, such as buprenorphine, a partial agonist that later became established as a key treatment for opioid dependence. In 1962, tramadol was synthesized and marketed in 1977; its dual mechanism of action (opioid and monoaminergic) led to widespread use in chronic pain. The co-ingestion of opioids in medication poisonings with suicidal intent significantly increases episode severity.[15]

However, from the 1980s onward, a parallel phenomenon emerged: the illicit production of fentanyl and its analogues. Episodes of mass intoxication in the United States due to compounds such as "China white" (3-methylfentanyl) foreshadowed a problem that, since 2013, has reached epidemic proportions.[16,17] The ease of synthesis, low production cost, and extreme potency of these substances have made synthetic opioids the core of the current overdose crisis in North America and, to a lesser extent, in other regions worldwide.[18]

During this synthetic opioid epidemic, naloxone has proven indispensable. In the United States and Canada, widespread distribution of naloxone kits to health care professionals, emergency services, people who use drugs, and their families has enabled the reversal of millions of overdoses. Two recent systematic reviews have shown that, as a central component of harm reduction strategies, several countries have implemented publicly funded programs for community-level naloxone distribution (to users, relatives, and police), demonstrating effectiveness in reducing opioid overdose mortality. All studies concluded that community naloxone distribution is cost-effective.

Nitazenes: The next emerging epidemic?

Nitazenes are a group of synthetic opioids first developed in the 1950s during the search for analgesics as alternatives to morphine. These compounds exhibited analgesic potency far exceeding that of morphine and other classical opioids, in some cases surpassing fentanyl. However, their narrow therapeutic index and high risk of dependence and toxicity prevented their commercialization as drugs.

After remaining dormant for decades, nitazenes have re-emerged in the illicit drug market, particularly since 2019. The first detected compound was isotonitazene, followed by analogues such as metonitazene, protonitazene, etonitazene, butonitazene, and clonitazene. These substances are relatively easy to synthesize and are often sold as heroin substitutes or used to adulterate other opioids, increasing inadvertent exposure among users.

Pharmacologically, nitazenes are potent μ-opioid receptor agonists with a marked capacity to induce respiratory depression, explaining their association with fatal overdoses in settings where users are unaware of their presence. Although naloxone is effective as an antidote for nitazene intoxication, cases requiring repeated or higher cumulative doses compared with heroin, morphine, or fentanyl have been reported due to their extreme potency. When hospital admission is required, length of stay is often longer than for other opioids. From a public health perspective, nitazenes represent a new challenge within the global opioid epidemic, with a profile similar to that previously observed with fentanyl and its analogues, and are already present in Spain.[19]

Conclusions

Naloxone, a pure opioid antagonist, has been fundamental to clinical toxicology and public health over the past 60 years due to its ability to rapidly reverse

respiratory depression in overdose patients. Its development and application are embedded within a long history of opiate and opioid use, from ancient opium consumption to the current synthetic opioid crisis. Naloxone use has expanded from hospital and prehospital emergency services to community-based programs and remains essential in reducing overdose-related mortality.

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