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Opioid Toxicity

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Continuing Education Activity

Pain is one of the most common reasons a patient seeks medical care. Various modalities may be used to relieve pain, and one of them is the administration of opiates. Opiates and opioids are strong pain relievers derived from the plant *Papaver somniferum*. Conventionally, the term "opiates" refers to natural compounds obtained from the poppy flower base, while "opioids" are synthetic agents with similar effects.

Opiates have been formally approved for analgesia for nearly 70 years, and these drugs have been assumed to be relatively safe despite the potential consequences of overdosing, including central nervous system and respiratory depression resulting in arrest. However, many reports in the last 2 decades have raised concerns about the safety of these drugs. Opiate prescriptions have dramatically increased over this period, with the United States currently experiencing an opioid epidemic with fatal consequences. Overdose and toxicity cases are on the rise and are continually reported in all major cities. Empirical prescription habits by healthcare workers to relieve pain have also led to an epidemic of overdose outside the healthcare setting, with the eruption of clandestine laboratories manufacturing synthetic opioids such as fentanyl and distributing them on the street.

This activity for healthcare professionals is designed to enhance learners' proficiency in evaluating and managing opioid toxicity. Participants gain a deeper understanding of the condition's risk factors, etiology, toxicology, pathophysiology, presentations, and evidence-based diagnostic and therapeutic strategies. The course highlights the use of opioid reversal agents such as naloxone to reduce morbidity and mortality. Emphasis shall be given to the role of healthcare professionals in treating opioid use disorder through medication-assisted and nonpharmacologic approaches to support recovery and abstinence. Greater competence equips clinicians to collaborate effectively within an interprofessional team caring for affected individuals, improving outcomes.

Objectives:

- Apply toxicokinetic data when evaluating the progression of opioid overdose and toxicity.
- Select the appropriate diagnostic tests to differentiate opioid overdose from conditions that can present with similar signs and symptoms.
- Implement individualized combinations of pharmacological and nonpharmacological treatments for managing opioid toxicity.
- Collaborate with the interprofessional team to educate, treat, and monitor patients with opioid toxicity to improve health outcomes.

Access free multiple choice questions on this topic.

Introduction

The term "opiate" refers to natural compounds derived from the base of the *Papaver somniferum* poppy flower, such as opium, morphine, diacetylmorphine (heroin), and codeine.[1] In contrast, opioids are synthesized through chemical processes and include methadone, oxycodone, and fentanyl. Opiates have been used since antiquity to relieve pain and induce euphoria. Today, these agents remain a widely used option for pain relief. Opiates have been formally approved for analgesia for nearly 70 years and have long been assumed to be relatively safe and nonaddictive when used for chronic pain.[2]

In 1995, Dr. James Campbell addressed the American Pain Society, advocating for the evaluation of pain as a vital sign.[3] His intentions were well-meaning, motivated by concerns about the undertreatment of pain. However, over the past 2 decades, numerous reports have raised alarms about the safety of these drugs. Cases of overdose and opiate toxicity are reported regularly across major cities in the United States. Particularly concerning is the dramatic increase in opiate prescriptions over the same period. This widespread prescribing by healthcare providers has contributed to an epidemic of overdoses outside the healthcare setting. Consequently, practicing healthcare professionals should recognize opiate toxicity in patients who present as lethargic or unresponsive without an apparent cause. (CDC, 2017)

Data released by the Drug Enforcement Administration (DEA) and the Centers for Disease Control and Prevention (CDC) indicate that, from 2001 through 2010, the rates of opiate diversion, opiate prescriptions, and opiate-related deaths exponentially increased in the United States. These rates plateaued from 2011 through 2013 but spiked again between 2013 and 2014. Experts in pain management believe that the high number of opiate overdoses is likely unintentional, as patients may have been attempting to manage unrelenting pain. (CDC, 2016)

Prescriptions for opioid-containing medications quadrupled between 1999 and 2010, paralleling a 4-fold increase in overdose deaths due to opioids. The majority of opioid-related deaths are attributed to the use of heroin and synthetic opioids other than methadone.

The issue of poorly treated pain has led medical professionals to use various short- and long-acting opiates. While this approach has significantly improved pain relief, some patients often fail to adhere to proper dosing. When patients increase the dose or duration of opioid use, toxicity becomes a potential complication. Although the annual rates of transition are low, toxicity often occurs when individuals move from the nonmedical use of prescription opioids to heroin.

Opioid overdose occurs when excessive unopposed stimulation of the opiate pathway leads to decreased respiratory effort and, potentially, death. The frequency of opioid overdoses is rapidly increasing. Drug overdose is now the leading cause of accidental death in the United States, with opioids being the most common culprit. According to the CDC, more than 1,000 emergency department visits reported daily are related to opioid misuse, and about 91 opioid overdose deaths are documented every day.

Heroin, priced at about $2 per bag, is up to 10 times cheaper and more readily available than prescription opioid medications purchased on the street, which average around a dollar per milligram. Additionally, heroin is increasingly being mixed with fentanyl and other synthetic opioid compounds, resulting in variable opioid potency and a higher risk of overdose.

Nonpharmaceutical or "street" opioids are often contaminated with other substances. To increase profits, sellers frequently add additional agents to the formula without informing the end user. These additives are pharmacologically active in many cases. Heroin was adulterated with scopolamine 2 decades ago in New York City, causing severe anticholinergic toxicity. Cocaine adulteration is also prevalent.[4][5][6][7]

Prescription Monitoring

Most states have established prescription drug monitoring programs (PDMPs) to counter the liberal prescribing of opiates by healthcare workers. In many states, healthcare professionals must consult the state's online drug database to determine which analgesic drugs may be prescribed to patients. Such state-enacted legislation aims to prevent mass opiate prescriptions by healthcare workers and to help stop the diversion of legitimate opiate prescriptions. (DEA, 2016) Results are mixed, but research suggests that opioid databases have reduced opioid prescribing. [8]

Additionally, with the assistance of the DEA, statewide registries of controlled substances now help healthcare providers track usage patterns among patients to identify people at high risk for opiate diversion or abuse. While the availability of opiates contributes to opioid addiction, no evidence has yet demonstrated a direct link between opiate abuse and the legitimate use of these drugs for pain. (DEA, 2016)

Etiology

Both opioids and opiates act on 3 major classes of opioid receptors: μ, κ, δ, and several minor classes, such as nociceptin and ζ. Simply put, μ-receptors are thought to provide analgesia, respiratory suppression, bradycardia, physical dependence, gastrointestinal dysmotility, and euphoria. Agonism of κ-receptors can lead to hallucinations, miosis, and dysphoria. The δ-receptor likely contributes to pain control and mood modulation, but some suggest that μ agonism is necessary for the δ-receptor to function effectively in analgesia.[9][10] Causes of opioid overdose include substance abuse, unintentional and intentional overdose, and therapeutic drug error.

The risk of opioid overdose increases in the following situations:

- Taking escalating doses
- Returning to use after cessation
- Having severe medical and psychiatric conditions, such as depression, HIV infection, and lung or liver disease
- Combining opioids with sedative medications
- Being male
- Being younger (20 to 40 years)
- Being of White non-Hispanic race [11][12]

More than 1.5 million emergency department visits are related to opioid analgesic use. Opioid overdose is a common cause of death.

Epidemiology

Impact of the Opioid Crisis in the United States

Opiates are frequently prescribed for moderate to severe pain in the United States. These drugs may be prescribed alone or combined with nonsteroidal anti-inflammatory drugs or muscle relaxants. Based on data from the Automation of Reports and Consolidated Orders Systems, the percentage increases in opiate use from 2004 through 2011 were as follows:

- Buprenorphine 2318%
- Fentanyl 35%

- Hydromorphone 140%
- Methadone 37%
- Morphine 64%
- Oxycodone 117%

Meanwhile, the use of codeine decreased by 20%.

Data from the Drug Abuse Warning Network (DAWN) has revealed that abuse of all the above opiates increased, with hydromorphone and buprenorphine leading the way with a 438% and 384% increase, respectively. (SAMHSA, 2014) Other reports from DAWN reveal that nearly 420,000 documented emergency room visits in 2013 were related to opiates. Cases of abuse and diversion of opiates over the past decade have included drugs like hydrocodone, hydromorphone, fentanyl, morphine, oxycodone, and tramadol.

In 2015, United States poison control centers reported a total of 18,425 exposures to pure opiates, which resulted in 68 fatalities and 764 cases of major toxicity. Additionally, 14,632 cases involved exposure to combinations of opiates with alcohol, benzodiazepines, aspirin, acetaminophen, or ibuprofen. The combined exposures resulted in 32 fatalities and 288 cases of severe toxicity. (AAPCC, 2017) The opioid crisis was reported to claim about 128 lives per day in 2018.[13]

Global Consequences of the Opioid Epidemic

The opiate toxicity epidemic is not limited to the United States but is also a worldwide concern. According to the 2014 United Nations Office on Drugs and Crime, at least 0.4% of the population, or nearly 20 million people, regularly use heroin or opium. The highest usage rates are found in Southwest Asia (1.21%), followed by Southeastern and Eastern Europe (0.83%), and Transcaucasia and Central Asia (0.81%).

In Europe, opioid-related deaths have been primarily linked to the illicit use of fentanyl and its analogs. In countries experiencing a heroin shortage, fentanyl and related products have replaced heroin as the illicit drug of choice. In Russia and Ukraine, desomorphine, known as "krokodil" on the street, is inexpensive and easy to produce from codeine. Besides being 10 times more potent than morphine, the unrefined synthesis methods cause skin abscesses, necrosis, and other life- and limb-threatening complications for users.[14]

Pathophysiology

Opioids exert their clinical effects by interacting with the opioid receptor, which has 3 subtypes: μ, κ, and δ. These receptors are all G-protein-linked and are found throughout the human body. Each subtype produces different clinical manifestations when activated.[15]

μ-receptors mediate analgesia, euphoria, sedation, respiratory depression, gastrointestinal dysmotility, and physical dependence. These receptors reduce the medullary response to hypercarbia and decrease the respiratory response to hypoxia, leading to a diminished stimulus to breathe and the development of apnea. μ-receptors are concentrated in the brain, where they regulate analgesia; in the mesolimbic system, which is responsible for euphoria and reward; and in the medulla, which regulates respiration.

κ-receptors mediate analgesia, diuresis, miosis, and dysphoria primarily within the spinal cord. Stimulation of this receptor subtype is not associated with constipation or significant changes in respiration. μ-receptor-specific antagonists do not reverse analgesia provided by κ-receptor stimulation.[16]

δ-receptors mediate analgesia, inhibit dopamine release, and suppress cough. Less is known about the stimulation of this receptor, but it is believed to play a smaller role in behavior reinforcement.

Opioids may be agonists, partial agonists, or agonist-antagonists of opioid receptors, which are located in the brain, spinal cord, and gastrointestinal tract. In overdose, excessive stimulation of the μ-opioid receptors in the brain that regulate respiratory rate leads to respiratory depression and, ultimately, death by respiratory arrest. The typical symptoms of overdose include pinpoint pupils, respiratory depression, and a decreased level of consciousness, which, together, form the "opioid overdose triad."

The roles of the σ- and δ-opioid receptors are less well understood. However, hallucinations, dysphoria, and psychosis may develop when σ-receptors are stimulated. Stimulation of δ-receptors can produce analgesia, euphoria, and seizures. σ-receptors are no longer considered opioids because they are not antagonized by naloxone.

Tolerance occurs rapidly with opioids. In overdose, patients often succumb to respiratory failure. Tolerance to the loss of the hypercarbia drive takes longer to develop than tolerance to other euphoric effects, but opioid-tolerant patients do not develop complete tolerance to the loss of the hypoxic stimulus, leaving them susceptible to death from overdose.[17][18][19]

Toxicokinetics

Opiates may be administered intravenously, topically, inhalationally, intramuscularly, and orally. Peak opiate effects are reached within 5 to 10 minutes following intravenous administration but may take up to 90 minutes if the oral route is used. Drugs like heroin and butorphanol can reach peak levels within 10 to 15 minutes after nasal insufflation and about 30 to 45 minutes following intramuscular injection. Fentanyl, which is the only available topical analgesic agent, often takes 2 to 4 hours to reach peak levels.

Most orally administered opiate is absorbed in the small intestine. Large opiate doses can lead to gastric aperistalsis and a delay in gastric emptying, resulting in increased absorption of the drug. Once in the body, opiates are metabolized by the liver into inactive compounds, which are primarily excreted by the kidneys. Opiates such as buprenorphine and fentanyl are highly lipid-soluble and tend to redistribute into fatty tissues, resulting in a prolonged half-life. Since all opiates are metabolized by the liver, they tend to have a long half-life when consumed in the presence of liver dysfunction (eg, cirrhosis). Opiate toxicity in patients with this condition can occur rapidly, even with small doses, as the drug remains in the body for an extended period.

The hepatic microsomal CYP2D6 enzyme breaks down codeine into the active metabolite morphine. Some individuals carry more than 2 copies of the enzyme, making them ultrarapid metabolizers who quickly convert codeine into morphine. These people may develop morphine toxicity if they take even normal doses of codeine. This same mechanism of ultrarapid breakdown explains why tramadol may also cause opiate toxicity. After being metabolized in the liver, opiate metabolites are excreted in the urine. Individuals with renal dysfunction may experience adverse effects from the accumulation of active metabolites, such as normeperidine. Several studies indicate that long-acting opiates used for noncancer pain may increase the risk of adverse cardiac events compared to tricyclics or anticonvulsants.

Formulas of Opiates and Delivery

In the past, opiates were only available in oral and injectable formulations. Today, dermal, sublingual, and inhaler formulas are also sold in the market. Butorphanol comes in an intranasal form, and fentanyl is available both as a topical and an inhaler.

The transdermal delivery of opiates like fentanyl has become widely accepted in healthcare settings for analgesic relief. This delivery route is preferred because drug levels take 4 to 6 hours to peak, and the elimination half-life is long, making it suitable for patients with chronic, continuous pain. Additionally, this route rarely precipitates toxicity because of the relatively prolonged, slow onset of action. However, the topical formulation of fentanyl can contribute to the toxicity of parenteral and oral opiates.

Dextromethorphan was once widely available in many over-the-counter cough preparations. However, this product is no longer sold without regulation because of diversion. Although dextromethorphan was an over-the-counter preparation, high doses were known to cause sedation and even respiratory depression due to its chemical similarity to codeine. Additionally, using dextromethorphan in combination with monoamine oxidase inhibitors can lead to life-threatening serotonin syndrome, which may result in adverse cardiac events.

Tramadol (Ultram) is classified as a nonopiate analgesic. However, this product has a dual mode of action, acting on both nonopiate and opiate receptors. Tramadol has a comparatively long duration of action, lasting 5 to 6 hours. Naloxone administration is recommended for patients known to have overdosed on tramadol, with most individuals requiring repeated doses or a continuous intravenous infusion.

Many clandestine laboratories have emerged across the nation due to the difficulty of legally obtaining prescription opiates. These laboratories operate under unsterile conditions and use impure substances, resulting in more toxic drugs being sold on the street. Another challenge with illicit drugs produced in clandestine laboratories is that many cannot be detected using standard toxicological screens because of their structural dissimilarities.

Several synthetic fentanyl derivatives, such as α-methylfentanyl, are circulating on the street and are extremely potent. Multiple deaths have been reported, with users found with needles still in their arms. Another synthetic derivative, 3-methylfentanyl, is thousands of times more potent than morphine. Extremely high doses of intravenous naloxone infusions are required for people overdosing on this agent. Deaths from these fentanyl derivatives often occur in clusters, as sellers move from street to street, causing multiple fatalities along the way.

Pentazocine is classified as a partial agonist-antagonist and is used to treat moderate to severe pain. This drug works by stimulating the κ-opiate receptors and inhibiting the μ-opiate receptors. The drug shares many adverse effects common to other opiates. However, a unique feature of pentazocine is its potential to cause nightmares, hallucinations, and delusions. Pentazocine has a high ceiling effect, meaning that a high dose must be reached before further drug administration stops providing additional pain relief, although the risk of side effects still increases. The pharmacological effects of pentazocine may be reversed by naloxone, but extremely high doses (10 to 115 mg) are required.

Propoxyphene is an opiate analgesic once prescribed to manage mild pain and cough. Sporadic cases of poisoning with this drug continued even after it was withdrawn from the American market in 2010 due to concerns about serious adverse cardiac events. Despite the ban, the drug remains available illegally and contributes to a significant number of poisonings each year. Naloxone can reverse the toxicity of propoxyphene but does not address the cardiac arrhythmias caused by the drug. These arrhythmias, resulting from the quinidine-like effects of propoxyphene, are unresponsive to naloxone. Propoxyphene can cause sinus bradycardia, heart block, and ventricular arrhythmias. Immediate treatment involves the administration of sodium bicarbonate.

The combination of diphenoxylate and atropine is commonly used to treat diarrhea. The opioid diphenoxylate acts as an antidiarrheal agent. The anticholinergic atropine is added to deter

deliberate misuse and overdose. Atropine itself has no antidiarrheal activity. High doses of this combination can cause primarily anticholinergic side effects, respiratory depression, and constipation. Cardiac toxicity, including prolongation of the QRS and QTc intervals leading to ventricular arrhythmias, is the main concern with the use of this drug combination.

Body Packers and Stuffers

Transporting illicit drugs in the body has become increasingly common over the past 2 decades. These individuals, often called "drug mules" or "carriers," ingest drugs contained in plastic bags or condoms. The number of packages ingested typically ranges from 1 to 3 dozen. Some may rupture despite being well-packaged, leading to systemic toxicity. Others may develop complications such as bowel obstruction and intestinal perforation, requiring surgery. Additionally, when pursued by law enforcement, these individuals may quickly swallow smaller quantities of drugs to evade arrest. Body stuffers are at a higher risk of adverse effects, as the drugs they transport are often improperly packaged. Symptoms can appear rapidly following ingestion, and aggressive medical intervention is often necessary to prevent overdose and death.

History and Physical

History

Most patients who overdose on opiates are lethargic or comatose. Thus, the history is typically gathered from family, friends, bystanders, or emergency medical service providers. Pills, empty bottles, needles, syringes, and other drug paraphernalia are often found at the scene. Important details to obtain in the history include the amount of drug ingested, congestion, and time of ingestion. In some cases, Emergency Medical Services (EMS) personnel may administer naloxone in the prehospital setting, which can help confirm the diagnosis of opiate overdose.[20][21][22][23]

Physical Examination

Patients with opiate overdose commonly exhibit lethargy or a depressed level of consciousness. Opiate overdose also leads to respiratory depression, generalized central nervous system (CNS) impairment, and miosis. However, healthcare workers must recognize that miosis is not always present in every patient with opiate overdose, and other causes of CNS and respiratory depression should be considered. Additional signs of opiate overdose include euphoria, drowsiness, altered mental status, fresh needle marks, seizures, and conjunctival injection.

Skin evaluation

Examination of the extremities may reveal needle track marks in individuals who abuse intravenous opiates. Many people with substance use disorders also inject morphine and heroin subcutaneously. In some cases, opium oil may be inhaled, and individuals may have patch marks on their bodies from fentanyl use. Most opiates can trigger the release of histamine, leading to itching, skin flushing, and urticaria.

Pulmonary assessment

In some morphine toxicity cases, respiratory distress and hypoxia may present with pupillary dilation. Additionally, drugs such as meperidine, morphine, propoxyphene, and diphenoxylate/atropine can cause midpoint pupils or frank mydriasis. Breathing is typically impaired in patients with morphine overdose. One may observe shallow breathing, hypopnea, and bradypnea, with a respiratory rate of 4 to 6 breaths per minute. Since opiates may also cause bronchoconstriction, some individuals may present with dyspnea, wheezing, and frothy sputum production.

Cardiovascular examination

Most opiates cause peripheral vasodilation, which can lead to moderate-to-severe hypotension. However, this hypotension may be reversed with changes in body position or fluid administration. Other coingestants must be considered if the hypotension is severe and unresponsive to fluids.

Gastrointestinal evaluation

Nausea and vomiting are common in patients with opiate toxicity. These symptoms occur because opiates can induce gastric aperistalsis and slow down intestinal motility.

Psychiatric features

Opiates are generalized CNS depressants. However, these drugs can also cause anxiety, agitation, depression, dysphoria, hallucinations, nightmares, and paranoia.

Neurological assessment

Opiates can lower the seizure threshold, potentially leading to generalized seizures, particularly in young children. This effect is mainly due to the paradoxical excitation of the brain. The opiates most commonly involved in adults experiencing seizures are propoxyphene and meperidine. Hearing loss may occur in rare cases, particularly in individuals who have consumed alcohol with heroin. However, this auditory deficit is usually reversible.

Evaluation

Opiate overdose or toxicity must always be considered in patients presenting with lethargy of an unknown cause. Many individuals who abuse opiates may concurrently use other illicit substances, such as cocaine, or prescription drugs, like antidepressants and benzodiazepines. Suspicion of coingestants should be raised when the usual clinical signs and symptoms of opiate toxicity are absent and the patient does not respond to the opiate antagonist naloxone.[24][25][26][27]

Laboratory Studies

Laboratory studies are often conducted for patients with drug overdoses. Drug screens are widely available but may not significantly affect initial management due to the high potential for false positives and negatives. In patients with opiate toxicity or overdose, the following blood work is usually performed:

- Complete blood cell count
- Comprehensive metabolic panel
- Creatine kinase level
- Arterial blood gas determinations
- Pregnancy testing
- Acetaminophen and salicylate testing

Imaging Studies

A chest x-ray should be obtained if lung injury is suspected. An abdominal x-ray or computed tomography should be obtained if the patient is possibly a body packer.

Electrocardiography

Electrocardiography (ECG) is recommended in all patients with suspected opioid overdose. Coingestants like tricyclics have the potential to cause arrhythmias.

Treatment / Management

Prehospital Management

Often, the first responder at the scene of a suspected opioid overdose is a nonmedical individual, such as a police officer. As of 2016, over 1,214 law enforcement agencies have trained their officers to administer naloxone in the field. This community involvement has led to increased survival rates following overdose incidents in the Midwest United States.[28]

Emergency medical technicians must be aware of prearrival naloxone administration by law enforcement and its effects. In some cases, patients may experience a complete reversal of toxicity and refuse further medical care or transportation to an emergency department. Studies have shown low short-term mortality rates in these cases. However, the potential risks of recurrent toxicity must be explained to these individuals, as well as the associated morbidity and mortality.[29][30]

If EMS are the first responders, priority should be given to assessing airway and hemodynamic stability. Naloxone should be administered in cases of decreased respirations. If the individual has no intravenous access, naloxone may be given intramuscularly, intranasally, intraosseously, or endotracheally via an endotracheal tube.

Data show that the intranasal route is as effective as the intramuscular route in the prehospital setting. However, naloxone may cause agitation and aggression when it reverses the opioid effects. The lowest naloxone dose necessary to reverse respiratory apnea should be administered in individuals with opioid use disorder (OUD). Patients may become combative or violent in the ambulance, and restraints may be needed for the safety of both the patient and EMS personnel. If the patient remains unresponsive to naloxone, endotracheal intubation should be considered to protect the airway.

Emergency Department Care

Immediate assessment of the patient's airway and hemodynamics should be given priority upon evaluation in the emergency department. Additional information from EMS personnel should include the presence of any drugs or paraphernalia, the patient's initial presentation (including vital signs), any potential trauma, and details regarding the timing and specifics of the suspected overdose. EMS personnel at the scene may have already secured the airway by administering naloxone or performing endotracheal intubation in some cases. Emergency physicians should evaluate the patient's airway and breathing upon arrival and determine if further intervention is necessary.

Immobilization should be prioritized if suspicion of occult trauma to the cervical spine arises. A capillary blood glucose level should be checked in any patient presenting with an unknown cause of lethargy or loss of consciousness, even if an overdose is highly suspected.

Initial treatment of overdose starts with supportive care, including assistance with respiration, cardiopulmonary resuscitation (CPR) in the absence of spontaneous circulation, and removal of any opioid agent, such as a patch or infusion. Naloxone should be administered immediately when an opioid overdose is suspected as the cause of respiratory and CNS depression, without delay for laboratory studies.

Naloxone administration

Naloxone is a pure competitive antagonist of opiate receptors and has no agonistic activity. The drug is relatively safe and may be administered intravenously, intramuscularly, subcutaneously, or endotracheally, though research on tracheal absorption has been conducted only in animal models. The Food and Drug Administration (FDA) has approved an intranasal formulation

commonly used by first responders in patients without intravenous access. Intranasal naloxone is also available to the community.[31]

After naloxone administration, the onset of action occurs within minutes, regardless of the route. A second dose may be given every 2 to 3 minutes. With subcutaneous or intramuscular injection, the onset may be delayed by 3 to 10 minutes. The goal of naloxone administration is to restore adequate breathing and ensure a stable airway. Higher doses are required for patients who overdosed on diphenoxylate, methadone, butorphanol, nalbuphine, or pentazocine. A naloxone infusion can be started in patients who need repeated doses to maintain respiration.

Nalmefene is a new agent on the market that can reverse opiate toxicity. This drug has a half-life of 4 to 8 hours. However, routine use of this longer-acting opiate antagonist is not recommended due to concerns about precipitating a prolonged period of opiate withdrawal.

Starting dose of naloxone

The usual starting dose of naloxone for adults ranges from 0.4 to 1 mg. Meanwhile, the starting dose for children is 0.1 mg/kg. The goal of naloxone administration is to reverse respiratory depression, not to "wake up" the individual. Naloxone should be administered slowly in suspected chronic opiate users, with doses of 0.04 to 0.4 mg given intravenously every 1 to 3 minutes. This approach ensures a more controlled reversal of opiate effects and reduces the risk of precipitating withdrawal symptoms.[32] Rapid administration of naloxone in these patients can trigger withdrawal, which is distressing for the patient and potentially places healthcare workers at risk of injury.

Before naloxone administration, the patient should receive 100% fraction of inspired oxygen assisted by bag-valve ventilation until they become more alert and cooperative or until naloxone is administered. The onset of naloxone’s action is immediate, with peak response occurring within 3 to 8 minutes. A repeat dose may be indicated if the patient continues to show signs of opiate toxicity.

Starting with a low dose of naloxone is important, typically 0.05 to 0.1 mg intravenously, gradually titrating upward to minimize the risk of withdrawal symptoms, such as nausea, vomiting, agitation, pain, and aspiration. This careful dosing is especially crucial in patients suspected of ingesting opiates combined with other CNS depressants such as alcohol, tricyclic antidepressants, and benzodiazepines. Peripheral intravenous access may be difficult in some patients with opiate overdose and long-term OUD. In such cases, 2 mg of naloxone may be administered intramuscularly or intranasally. Even with this route, opiate toxicity is reversed within 5 to 10 minutes.

The half-life of naloxone is about 30 to 45 minutes, with a duration of action ranging from 90 to 180 minutes. These variations depend on the route of administration and dose. Patients should be monitored for any recurrence of opioid toxicity, as the initial drug effect may last longer than naloxone’s duration of action. An infusion may be started in patients requiring multiple bolus doses. The naloxone infusion dose is 3/4 of the amount required to reverse respiratory depression.[33]

Much higher doses of naloxone are usually needed to reverse toxicity in patients who have taken large doses of propoxyphene, methadone, diphenoxylate/atropine, or fentanyl. Repeat doses of 2 mg may be required every 3 to 4 minutes for a total of 10 mg. The diagnosis of opioid toxicity should be reconsidered in patients who fail to respond to 10 mg of naloxone. Many street opiate preparations are adulterated, and the response to naloxone may not always be complete. A steady naloxone infusion is generally preferred over intermittent dosing for treating large overdoses. However, a naloxone infusion should not be administered if intubation is necessary.[34][35][36] Clinicians must be ready to intubate if the patient remains in respiratory distress.

Role of activated charcoal

Activated charcoal may be used to decontaminate the gastrointestinal tract in cases of oral opiate overdose, such as with body stuffers, if the patient is alert at the time of admission. Activated charcoal is typically effective only if administered within 1 hour of drug ingestion. However, opiates slow gastric motility, allowing activated charcoal to be given up to 2 to 3 hours after ingestion. Activated charcoal should be considered for all patients with opiate overdose in the absence of contraindications, such as vomiting and decreased mental status.

Activated charcoal should not be administered to patients with depressed mental status or any individual with airway concerns. Patients should not be intubated solely to administer activated charcoal.

Bowel irrigation

Whole bowel irrigation may be considered for individuals who have ingested drug packets containing opiates, as in the case of a body packer. However, no controlled studies confirm that this treatment offers any benefits or improves outcomes. Whole bowel irrigation is not recommended for patients showing signs of ileus, bowel obstruction, peritonitis, hemodynamic instability, or an unprotected airway.

Additional measures

Some patients with opiate toxicity may not respond to high-dose naloxone treatment. Anecdotal reports suggest that buprenorphine may be beneficial if the cause is determined to be an opiate and the patient is in respiratory arrest.

Intranasal administration of naloxone

Naloxone is highly effective when administered promptly, but its use has traditionally been limited to physicians and paramedics. With the rise in opioid overdoses, intranasal medication administration by bystanders is currently being advocated. Evidence supporting the efficacy of out-of-hospital naloxone administration is promising. The bioavailability of concentrated naloxone nasal spray has been shown to be around 25%. Fifty percent absorption occurs within 6 to 8 minutes, with maximum blood concentration reached at 20 minutes, making it a viable option for community and prehospital use.

A retrospective study of Basic Life Support (BLS) crews administering prehospital intranasal naloxone over 6 years found that 95% of patients who received treatment showed clinical benefits before arrival. Less than 10% of patients required additional doses in the emergency department, and 70% were eventually discharged.

Opioid poisoning in children

The dose of naloxone for children who are younger than 5 or weigh less than 20 kg is 0.1 mg/kg. For children who are older than 5 or weigh more than 20 kg, the dose ranges from 0.1 to 0.2 mg/kg. Repeat dosing may be required every 3 to 4 minutes, up to a maximum cumulative dose of 10 mg of naloxone. Repeat dosing is often necessary when the child has ingested longer-acting opiates like methadone. A continuous naloxone infusion may be started, but caution must be taken to avoid overhydration, which could lead to pulmonary edema. The pharmacy may assist with determining the correct concentration of fluid and naloxone for safe administration, but repeat bolus dosing may be safer if a concentrated infusion is unavailable.

Use of combined buprenorphine and naloxone

Buprenorphine, in combination with naloxone, is widely available and used to treat OUD in the outpatient setting. Buprenorphine acts as a partial agonist and antagonist at the opioid receptor.

Anecdotal data indicate that the risk of overdose is lower with buprenorphine/naloxone compared to methadone. Naloxone has no oral bioavailability and is included in the formulation to deter intravenous use. Unfortunately, the sublingual preparation of buprenorphine and naloxone may also be easily abused.

Naloxone adverse effects

Naloxone has demonstrated a very safe side effect profile. Studies on opioid-naive patients who received large doses of the drug showed no significant effects. However, naloxone can trigger acute opioid withdrawal symptoms in opioid-tolerant patients. These symptoms may include sudden aggression, agitation, restlessness, diaphoresis, tachycardia, and gastrointestinal effects such as nausea and vomiting, which occur in approximately 30% of patients. Most symptoms are mild and short-lived, with fewer than 1% of patients requiring admission. Acute withdrawal is more likely with higher doses of naloxone.

A rare but potential side effect of naloxone is noncardiogenic pulmonary edema, which is thought to result from a sudden catecholamine surge, typically following the administration of high doses of naloxone. Treatment involves positive pressure ventilation, starting with bilevel positive airway pressure (BiPAP) and escalating to endotracheal intubation if necessary.[37]

Inpatient Care

Most patients who overdose on opiates and experience a reversal with naloxone are admitted for observation for at least 12 to 24 hours. Naloxone's duration of action is approximately 1 hour, and long-acting opiates may continue to cause sedation and respiratory depression. These patients are best monitored on a specialized floor. The majority of patients on heroin overdose are admitted due to the risk of acute lung injury, which often presents early. Individuals who are asymptomatic after a heroin overdose may not require 24-hour monitoring but still need 6 to 12 hours of observation before discharge, provided their vital signs remain stable.

Admission is also recommended for patients requiring multiple doses or prolonged intravenous infusions of naloxone to maintain respiratory function. Admission is the safest course of action if the patient’s clinical stability is in question.

Outpatient Care

Given the association of opiate use with sudden respiratory difficulty, many healthcare professionals now advocate for take-home naloxone. Having naloxone at home is particularly beneficial for individuals at high risk of narcotic overdose.

Mainstreaming Addiction Treatment Act

The Mainstreaming Addiction Treatment (MAT) Act updates federal guidelines to expand access to evidence-based treatments for the opioid epidemic. This act enables all healthcare providers with a standard controlled substance license to prescribe buprenorphine for OUD, similar to how they prescribe other essential medications. The MAT Act aims to reduce the stigma surrounding OUD treatment and promote its integration into general healthcare settings.

The MAT Act has eliminated the DATA-Waiver (X-Waiver) program as of December 2022. DEA-registered practitioners with Schedule III authority are now permitted to prescribe buprenorphine for OUD within their practice, provided it aligns with applicable state laws. The Substance Abuse and Mental Health Services Administration (SAMHSA) encourages providers to take advantage of this change. Practitioners previously registered under the DATA-Waiver program automatically receive updated DEA registration certificates reflecting this change, with no action required on their part.

Practitioners are no longer limited in the number of patients with OUD they may treat with buprenorphine. Additionally, separately tracking patients treated with buprenorphine or the number of prescriptions written is not required.

Pharmacy staff can now fill buprenorphine prescriptions using the prescriber's DEA number without requiring a DATA 2000 waiver. However, depending on the pharmacy, dispensing software may still prompt for X-Waiver information to proceed. Practitioners must also adhere to any applicable state regulations regarding the treatment of patients with OUD. Contact information for State Opioid Treatment Authorities can be found here: https://www.samhsa.gov/medicationassisted-treatment/sota.

Differential Diagnosis

The differential diagnosis of opioid poisoning includes conditions presenting with sudden-onset respiratory or CNS depression, as follows:

- Barbiturate toxicity
- Benzodiazepine toxicity
- Carbon monoxide toxicity
- Clonidine toxicity
- Cyanide toxicity
- Diabetic ketoacidosis
- Ethanol toxicity
- Ethylene glycol toxicity
- γ-Hydroxybutyrate toxicity
- Hypercalcemia
- Hypernatremia
- Hypothermia
- Hypoglycemia
- Meningitis/encephalitis
- Neuroleptic agent toxicity
- Traumatic brain injury
- Valproic acid toxicity

Efficient and thorough evaluation of these alternative diagnoses ensures timely intervention and better outcomes.

Prognosis

Mortality and Morbidity

Death from opioid overdose is on the rise. One study found that deaths from opioid-only overdose increased by 384% between 1999 and 2018. Polysubstance overdose deaths increased by 760% over the same period in adolescents and young adults.[38] According to the CDC, nearly 108,000 individuals succumbed to opioid overdose in 2022. The COVID-19 pandemic response also led to an increase in mortality, as it limited access to treatment services.

The primary cause of morbidity and mortality following an opiate overdose is respiratory arrest. Seizures, acute lung injury, and adverse cardiac events may also occur but are less common. Individuals with preexisting lung pathology who overdose on opiates face a significantly higher risk of respiratory distress and death compared to the general population. Another factor contributing to opiate toxicity is the presence of coingestants, with the eventual toxicity depending on the type of substance involved. A Canadian study found that the risk of fatal opiate toxicity doubled when opiates were taken with gabapentin, which is also known to depress respiration. Additionally, morbidity and mortality are influenced by the intent behind the opiate ingestion. Individuals attempting suicide often consume multiple drugs simultaneously, substantially increasing the risk of death.

Prognosis

If the patient does arrest in the setting of a pure opiate overdose, the cause in most cases is severe hypotension, hypoxia, and poor brain perfusion. The outcome for these individuals is poor.

Complications

Opiate toxicity can also produce complications beyond the typical respiratory and CNS adverse effects.[39][40][41] The most common ones are discussed in this section.

Acute Lung Injury

Acute lung injury is a well-known complication of heroin overdose. However, this condition may also occur after overdoses involving methadone and propoxyphene and is almost universally observed in patients who succumb to high doses of opiates. The exact mechanism by which opiates cause lung injury remains unclear, but the outcome is hypoventilation and hypoxia caused by noncardiogenic pulmonary edema.

Clinically, heroin-induced lung injury presents with sudden onset of dyspnea, frothy sputum production, cyanosis, tachypnea, and rales—symptoms consistent with pulmonary edema. Acute lung injury has also been reported in children who ingest high doses of opiates. The presentation is very similar to acute respiratory distress syndrome (ARDS), and most cases resolve with aggressive airway management and oxygen therapy, including positive pressure ventilation. Standard medications for pulmonary edema are typically avoided, as diuretics may worsen hypotension.[42]

Infection

Complications of intravenous opioid use include abscesses, cellulitis, and endocarditis. Gram-positive bacteria, such as *Staphylococcus* and *Streptococcus,* are the most common organisms involved. If these bacteria enter the systemic circulation, the risk of additional complications like epidural abscess and vertebral osteomyelitis increases. These conditions often present with symptoms such as fever and persistent back pain.

Some individuals who inject drugs directly into the neck risk developing jugular vein thrombophlebitis, Horner syndrome, and pseudoaneurysms of the carotid artery. Both peripheral and pulmonary emboli have been reported in people who inject opioids. Accidental injection into nerves may also cause permanent neuropathy.

Endocarditis is a serious complication of intravenous drug use, often resulting from injecting illicit drug mixtures with contaminated needles. Diagnosing infectious endocarditis can be challenging due to the initially vague symptoms. While right-sided heart valves are most commonly affected, left-sided valves may also be involved in some cases. The tricuspid valve is the valve most frequently affected in individuals who use intravenous

drugs. Endocarditis often presents with fever, malaise, and a new murmur. In some patients, recurrent septic pulmonary embolism may be the only presenting feature.

The organism most commonly involved in right-sided endocarditis is *Staphylococcus aureus*. In contrast, left-sided endocarditis may be polymicrobial, involving organisms such as *Streptococcus*, *E. coli*, *Pseudomonas*, and *Klebsiella*. Symptoms and signs tend to be more pronounced in left-sided endocarditis compared to right-sided cases.

Other infectious manifestations of opioid abuse include recurrent pneumonia, with aspiration pneumonia occurring in some unconscious individuals. Necrotizing fasciitis, another life-threatening complication, often presents with severe pain, fever, and dark, dusky skin with crepitus. The individual may show signs of septic shock. Aggressive resuscitation and immediate surgical debridement can be life-saving.

Musculoskeletal and Neurologic Sequelae

Rhabdomyolysis is a relatively common complication of opioid overdose that may occur even without compartment syndrome. Opioids are likewise known to increase the risk of seizures, particularly drugs like propoxyphene, meperidine, pentazocine, intravenous fentanyl, and heroin. The individual may present with a prolonged seizure, which may result from CNS hypoperfusion and hypoxia or from intracranial injury due to a fall.

Narcotic Bowel Syndrome

Narcotic bowel syndrome is a type of opiate-induced bowel pathology characterized by frequent episodes of moderate-to-severe abdominal pain that worsens with escalating or continued opiate doses. This syndrome typically occurs in individuals without prior bowel pathology and represents a maladaptive response. Narcotic bowel syndrome may also be associated with intermittent vomiting, abdominal distension, and constipation. Eating tends to aggravate the symptoms, which can last for days or weeks. Anorexia may result in weight loss, and delayed gastric emptying and intestinal transit are delayed.

The syndrome is often mistaken for bowel obstruction. The key to diagnosis lies in recognizing that continued and escalating opiate doses worsen abdominal pain rather than provide relief. Treatment for narcotic bowel syndrome involves psychotherapy, as well as tapering or discontinuing the opioid. Successful treatment depends on developing a strong patient-physician relationship and trust, gradually withdrawing the narcotic, and using nonpharmacological treatments to manage pain.

Withdrawal Reaction

Withdrawal symptoms following cessation of opiates are common, but they are often vague and less severe than those observed with alcohol or benzodiazepine discontinuation. The onset of symptoms depends on the drug ingested, typically occurring within 2 to 4 days after methadone cessation and 8 to 10 hours after meperidine withdrawal. Autonomic symptoms may include excessive lacrimation, sweating, piloerection, rhinorrhea, repeated yawning, myalgia, nasal congestion, diarrhea, and abdominal cramps. Symptoms usually peak between 36 and 48 hours and gradually subside within 72 hours.

Symptoms may last 7 to 14 days in chronic drug addicts. Treatment for withdrawal symptoms is supportive, and the use of additional opiates to counter withdrawal symptoms is not recommended. Clonidine may be used in severe withdrawal cases, especially when methadone is inappropriate or unavailable. After acute treatment, the patient should be referred to a long-term drug rehabilitation program to help prevent relapse.

Deterrence and Patient Education

In early 2015, the U.S. Department of Health and Human Services acknowledged the expanded use of naloxone among healthcare professionals to counter opiate overdoses nationwide. Now, pharmacists, EMS personnel, and physicians can all play an active role in preventing opiate overdoses. Current recommendations also suggest coprescribing naloxone to patients taking opiates. Several studies show that patients who receive naloxone alongside an opiate prescription have fewer opiate-related emergency room visits than those who do not. Today, some healthcare workers have started prescribing naloxone to patients on high doses of opiates.

Recently, the U.S. Food and Drug Administration approved the use of a handheld autoinjector that can be prescribed to caregivers or family members for managing suspected opiate overdoses. Additionally, numerous naloxone organizations have emerged across the country to fight the opiate overdose epidemic, including efforts to involve nonmedical professionals like law enforcement officers.

Enhancing Healthcare Team Outcomes

With the drastic increase in opioid abuse and overdose-related deaths, much attention has focused on this so-called "opioid epidemic." All healthcare workers, including nurse practitioners who prescribe controlled substances, have a role in reducing the opioid epidemic and should be equipped to identify and treat those experiencing toxicity and overdose.

New research focuses on finding effective interventions and identifying risk factors for overdose. Some of these efforts include treatment programs, take-home intranasal naloxone, and monitored injection facilities. A review of research exploring overdose education and naloxone distribution suggests reduced fatality rates for patients who receive counseling and prescriptions for home naloxone.

Naloxone has been shown to have a very safe side effect profile. Several studies on opiate-naive patients who received large doses of the drug showed no significant effects. However, acute opioid withdrawal symptoms may develop when this agent is administered to opioid-tolerant patients. Individuals given naloxone in the setting of opioid overdose may experience sudden withdrawal syndrome, manifesting as aggression, agitation, restlessness, diaphoresis, and tachycardia. Gastrointestinal symptoms such as nausea and vomiting also occur in about 30% of patients. Most symptoms are not severe or sustained, and less than 1% of patients require admission. Acute withdrawal symptoms are more likely with larger doses of naloxone. Despite the risk of precipitated withdrawal, naloxone should not be withheld in cases of acute opioid overdose with respiratory depression.[43][44]

An interprofessional approach should involve physicians, nurses, and substance abuse counselors. The goal of the collaborative efforts of this group is to reduce morbidity and mortality associated with OUD.

Review Questions

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