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FEATURE ARTICLE

PEER REVIEWED

Recognizing Dangerous Poisonings in Primary Care: Part 4, Opioids

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The 5 most common causes of poisoning-related fatalities in the United States are antidepressants, antihistamines, cardiovascular drugs, opioids, and pesticides.[1] Drug poisonings, particularly mild cases, are often exceptionally difficult to recognize. Slightly dilated pupils, mild tachycardia and hypertension, slight fever, and tachypnea are all constitutional symptoms that fit myriad working diagnoses, but autonomic instability is a hallmark of drug poisonings. Motor stiffness and hyperreflexia are frequently seen with a number of drug poisoning syndromes, although not with pesticide poisoning.[2,3]

This 6-part review article series helps sort out some of the more common symptoms, interactions, and therapeutic considerations in the clinical approach to a patient whom you suspect may be experiencing the effects of the most common types of poisoning.

This article, the fourth in the series, covers opioid poisonings. Other articles in the series cover antidepressants, antihistamines, cardiovascular drugs, and pesticides, and one article specifically covers serotonin syndrome.

Opioids are a broad class of drugs that include therapeutic medications as well as illegal substances of abuse. There are naturally occurring, synthetic, and semisynthetic compounds that are classified as opioids.

The use of opium, one of the oldest known substances used for therapeutic purposes, dates to 4000 BCE, when it was originally thought to have been isolated from poppies. Morphine, the representative drug of the class, was first isolated from opium in Germany in the early 1800s by Friedrich Sertürner. Various other alkaloids were isolated or synthesized thereafter, notably heroin in 1898. These substances have since become increasingly popular for use in medicine and for recreational use.

The pharmacologic actions of opioids act on several organ systems, including the central nervous system (CNS) and the cardiovascular, respiratory, and gastrointestinal systems. Sedation and analgesia are the main uses for opioids; however, they are also valued for their ability to decrease cough and gastrointestinal tract motility.[4]

The dangers of opioids have long been recognized since the use of opium thousands of years ago. Toxicity and acute overdose can be life-threatening, and the incidence of these episodes has been increasing around the world. In 2010, it was estimated that 58% of the US population between 15 and 64 years used prescription opioids, and that the mortality rate of dependent users is 6 to 20 times higher than in the general population. Of the approximately 40,000 drug overdose deaths in the United States in 2010, 58% involved pharmaceutical drugs, and opioids were involved in 75% of these deaths (the highest prevalence of any pharmaceutical, trailed by benzodiazepines and antidepressants, which were involved in 29% and 18% of these deaths, respectively). Most of these deaths were accidental (74%) and involved a combination of drugs

rather than a single drug class used alone.[5,6] Between 2001 and 2014, there was a 3.4-fold increase in the total number of US deaths involving prescription opioids alone; this number represents more than 18,000 potentially preventable deaths.[7] These statistics demonstrate the significant role that opioids play in current health care practices and in culture. Opioids are also one of the most lethal illicit drug classes, commonly causing lethal overdoses in young male users.[4] The annual mortality rate for active heroin users is 2%, and it is estimated that 8% of all illicit drug-related emergency department visits are related to heroin.[4]

There are many opioids, all of which are classified into 3 different groups. Exogenous opioids are those derived from the environment, most notably those from the opium poppy *Papaver somniferum*. These drugs include morphine, codeine, thebaine (precursor to oxycodone and naloxone), and papaverine. The second classification group is the synthetics, which include meperidine, diphenoxylate, loperamide, fentanyl, methadone, pentazocine, buprenorphine, and heroin. There are also naturally occurring endogenous opioids that include endorphins, enkephalins, dynorphins, and neuroendorphins. On a molecular level, these drugs interact with 3 main opioid receptors: stimulation of *μ*-receptors produces analgesia, respiratory depression, sedation, euphoria, miosis, and addiction; stimulation of κ-receptors produces spinal analgesia, dysphoria, sedation, and psychotomimetic effects (delusions and delirium); and stimulation of δ-receptors produces spinal analgesia, affective behavior, respiratory depression, reduced gastrointestinal tract motility, and urinary retention. The μ-receptors are responsible for most of the analgesic effect of opioids and are the class of receptors for which naloxone shows the most selectivity for competitive antagonism.

Opioids are administered via several routes, including oral, parenteral, transdermal, transmucosal, epidural, subarachnoid, intrathecal, intranasal, and inhalational. Heroin is usually abused through intravenous, subcutaneous, or inhalational routes. It is worth noting that toxicity via the gastrointestinal route is often less severe, although more prolonged, with a variable reduction in bioavailability depending on drug properties and first-pass metabolism. First-pass metabolism is the mechanism whereby the concentration of a drug is reduced before it reaches the systemic circulation, typically by absorption from the gut via the portal vein into the liver, where it is initially metabolized. Most opioids have a large volume of distribution (the hypothetical volume required if the amount of drug in the body were to be distributed throughout the body at the same concentration measured in the blood), and cross the blood-brain barrier into the CNS at different rates depending on the specific drug's lipid solubility. All opioids subsequently undergo hepatic metabolism and renal excretion of the conjugated glucuronides (many of which also have narcotic activity). Individual differences/genetic variations in hepatic enzymes (eg cytochrome P450) or kidney function may lead to increased or decreased risk of toxicity in certain individuals. Drug interactions may also have an effect on hepatic metabolism and need to be considered when evaluating a patient.[4,6]

As a class of drugs, opioids all elicit similar effects on the human body. The classic opiate toxidrome includes miosis, respiratory depression, CNS depression, and decreased gastrointestinal motility, however, each drug has varying toxicity profiles. The patient populations at risk are those who are younger than 65, have a history of substance abuse, have mental health disorders, or have chronic pain.[4]

Neurologic complications are common in opioid toxicity due to CNS and respiratory depression. Seizures, myoclonus, and hypertonicity may be seen, as well as disinhibitory excitation effects in certain users. Parkinsonian effects and spongiform leukoencephalopathy may be seen in long-term users of illicit meperidine analogues and heroin users, respectively. Additionally, serotonin syndrome should be suspected if the patient presents with mental status changes, autonomic instability, and neuromuscular changes. Serotonin syndrome occurs when the patient is taking an opioid that inhibits serotonin reuptake (eg, meperidine, dextromethorphan, methadone), along with a selective serotonin-reuptake inhibitor or a monoamine oxidase inhibitor.

Both serotonin syndrome and opioid toxicity (particularly with synthetic opioids such as tramadol) may produce similar signs including hypertonicity, myoclonus, and mental status changes. In situations where the diagnosis is unclear, clinicians should pay particular attention to the pupils, which are frequently mydriatic in patients with serotonin syndrome and miotic in opioid toxicity.Respiratory depression is the most letha

l effect of opioids, caused by suppression of the medullary respiratory center, which produces a decrease in the brain's sensitivity to rising carbon dioxide levels in the blood and a decrease in respiratory rate and tidal volume. In severe overdose, apnea, bronchospasm, or acute lung injury may occur. When mild orthostatic hypotension and bradycardia are encountered, returning the patient to a supine position often improves perfusion.[4,6] These effects are mostly histamine-mediated and may be reduced with the use of antihistamines.

In treating patients with opioids if hypotension is a concern, fentanyl, because it produces minimal histamine release, has been shown to have the least effect on blood pressure of all the narcotics.[8] Therapeutic and toxic doses of opioids often lead to nausea and vomiting, delayed gastric motility, constipation, and ileus. In long-term tolerant users, withdrawal is a risk if use is discontinued or an opioid antagonist is administered. The opposite effects of toxicity are seen, specifically increased sympathetic and adrenergic activity that lead to mydriasis, CNS excitation, tachypnea, vomiting, and diarrhea. Withdrawal may lead to dehydration and electrolyte abnormalities but is not usually lethal.[4,6]

Diagnosis of opioid toxicity is clinical and based on the history and physical examination findings; however, several laboratory tests should be ordered when toxicity is suspected. A fingerstick blood glucose test should be administered, since hypoglycemia may mimic an opioid

fingerstick blood glucose test should be administered, since hypoglycemia may mimic an opioid toxidrome. Pulse oximetry and blood gas test results will aid in assessment of respiratory status, while a chest radiograph will help assess for acute lung injury or aspiration pneumonitis. Electrolytes, creatinine kinase, an electrocardiogram, and urinalysis may be helpful in assessing certain patients.[4]

When opioid toxicity is suspected, the patient's respiratory status should quickly be assessed and managed. A bag-valve mask with supplemental oxygen often is adequate in maintaining ventilation until an opioid antagonist can be administered; however, endotracheal intubation is indicated if the intoxication is severe or if there is aspiration risk (eg, when a patient is comatose).

Naloxone is the most commonly used opioid antagonist in patients with suspected overdose. It is a pure opioid antagonist with rapid onset of action that leads to reversal of the opioid toxic effects. Ideally, a large enough dose should be given that will reverse the opioid toxicity without precipitating acute withdrawal. An initial dose of 0.04 to 0.20 mg should be given to suspected opioid-dependent patients, while a dose of 0.4 to 2.0 mg is the initial dose for nondependent patients. Pediatric dosing of naloxone is 0.1 mg/kg up to 2.0 mg. Naloxone can be administered by intravenous, subcutaneous, intramuscular, endotracheal, intranasal, and subcutaneous routes, with repeat dosing every 20 to 60 minutes as needed. After initial treatment, the patient should be observed in the hospital for at least 4 to 6 hours, and for 24 hours in cases of severe overdose.[4,6]

When discussing opioid toxicity with patients, prevention and education are important components to address. Various programs have been implemented in an attempt to reduce opioid-related deaths and overdoses. The Drug Enforcement Administration implemented the National Take Back Initiative in 2010, which designates locations and providers where unwanted prescription medications can be brought for proper disposal. Another successful program that targets reduction of prescription drug abuse are prescription drug monitoring programs, which allow prescribers to closely monitor their patients' prescription history and habits. Community-based naloxone take-home programs have been gaining traction in recent years, as well. San Francisco's DOPE (drug overdose prevention and education) project, which prescribes naloxone at area needle exchanges while providing opioid toxicity education, has shown significant trends in reducing opioid overdose deaths.[9] These programs, along with other tools such as urine drug testing, regular office visits, and restricted early refills, are ways in which clinicians can reduce the risk of opioid abuse and overdose.[10]

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