OPIOID TOXICITY

Objectives

When the student has finished this module they will be able to:

1. Explain how opioids work; specifically, what receptors they bind to and if they have an enhancing or inhibiting effect.
2. Identify the three cardinal signs of an opioid overdose.
3. Identify three *side effects* of opioids
4. Give two reasons why opioids cause hypotension.
5. Give two reasons why opioids cause respiratory depression
6. Identify the unique toxic effect of propoxyphene
7. Identify the therapeutic goal of naloxone administration.
8. Identify two reasons why hypothermia can be a feature of heroin overdose.
9. Identify the proper decontamination technique for body packers or body stuffers.
10. Explain how naloxone is administered as a continuous infusion.

Introduction

Opioid toxicity and poisoning is an enormous problem. In 2004, heroin was involved in over 162,00 drug-related emergency room visits.[1] According to the 2003 National Survey on Drug Use and Health, approximately 3.7 million Americans had used heroin some time in their lives and approximately 120,000 reported use of the drug in the month prior to the survey.[2] Worldwide opium production has more than doubled from 2002 to 2003, and admissions to treatment facilities for heroin addiction rose from 168,000 in 1992 to 285,000 in 2002.[3] Not only is heroin an enormous public health problem, the problem is growing.

This module is about opioids and opioid toxicity. There are many opioids and most of them are abused, but heroin is the most commonly abused opioid and much of the discussion in this module will focus on heroin.

History

The abuse of opium and opium-derived products is a very old one (Note: through the text, the word opioid will be used. This word indicates that the drug is a synthetically or semisynthetically derived derived opium product. Opiates are drugs that are derived directly from the opium poppy, eg, morphine, and codeine). The opium poppy has been cultivated for thousands of years and it has been used medicinally for thousands of years. Opium and opium-derived drugs were available for many, many years in the United States without a prescription and by all accounts, use was widespread and there were many addicts. It is easy to understand the popularity of opium. For physicians, it was one of the few effective medicines they could offer to their patients, and they used it to treat fever, diarrhea, pain, and as a sedative. It was also more benign, less dangerous, and less painful than some of the standard therapies of the day (eg, bleeding). For the working class, opium-containing product were cheap – much more so than a visit to a doctor – and apart from its medicinal properties it had other uses. It was used as a recreational drug, and it was commonly given to infants to control diarrhea, keep children manageable, and to curb appetite.[4] It was also used for infanticide (and this practice of using opium to kill children is very old. To get rid of unwanted children, Roman women would smear opium on their breasts then nurse the child).

Widespread public awareness of addiction as a social and health issue began to grow after the Civil War. Opium was in wide use by both armies; the Union dispensed more than 10 million opium pills and more than 2 million opium preparations in the form of powders or tinctures. The association of the Civil War with morphine addiction became so strong that addiction was called soldiers' disease or the army disease, and it was an epidemic that the medical establishment could not treat. Still, opium based products continued to be sold without a prescription until 1914 when the Harrison Narcotic Act was passed. This did not outlaw the use of narcotics, but it required doctors and pharmacists to keep records of the use and sales of these drugs and banned non-medicinal use of opium, and in 1924, the Heroin Act made the use and manufacture of heroin, even for medical uses, illegal.

Opium is derived from the opium (the word opium is derived from the Greek word *opos*, which means juice) poppy, *papaver sominiferum* (papaver is the Greek name for poppy and somniferum is a Latin word meaning sleep inducing.) The plant is grown legally in many parts of the world and illegally in South America, the Middle East and southeast Asia. It grows to approximately 2-5 feet tall and when it has matured, the plants are tapped, a very tiring and labor-intensive process. A small, specialized, three-bladed knife is used to make an incision (and this must be done at the correct time of day and at the proper depth) in the seedpod that grows at the top of the plant, and the milky sap that contains the opium flows out. Once it contacts air it turns into a dark brown, thick, sticky substance and it is scraped off the pod; this process may continue for several days. The opium is dried in the sun for several days to diminish water content, then it is placed in boiling water to further purify it and when this is done, it is molded into dense blocks, and it is ready to be refined into morphine or other opioids.[5]

Morphine (so named for the Greek god of sleep and dreams, Morpheus) was first refined from opium in 1804. It is the most prevalent alkaloid in opium, accounting for about 10-16% of the total weight of raw opium. Opium may be sold in its original form,

but it is bulky, difficult to transport, and is less popular than morphine or heroin. Converting opium into morphine is a simple process consisting of liquid phase chemical reactions that result in precipitates that are further strained, filtered, purified, etc. The opium is dissolved in hot water, lime is added to precipitate the non-morphine alkaloids and then ammonium chloride is added to precipitate the morphine alkaloid. When the process is finished, the morphine is ready to be converted into heroin. Making heroin from morphine is also relatively simple. The morphine is mixed with acetic anhydride and heated. After several hours, a crude form of diacetylmorphine – heroin – is produced. Several more steps subsequently purify this, heroin base is produced, and the base is sent to purifying labs where it is prepared for street sale.[6]

Heroin (the word is derived from the German word *heroisch,* meaning heroic; the first test subjects to whom heroin was given said it made them feel heroisch) was first synthesized as diacetylmorphine in England in 1874. However, over the next 20 years or more, the alkaloid was forgotten, overlooked, or used and found to be less effective than morphine. Then in 1897, a chemist working for the German pharmaceutical company, Bayer, in an attempt to remove some of the side effect of diacetylmorphine, acetylated the compound and heroin, in the form we know it today, was born. It was commercially marketed in 1899 as a powerful antitussive, and it was hoped it could be used for patients with tuberculosis and pneumonia; at the time, it was believed it slowed respirations but increased the force of each breath (and in this respect it was compared to digitalis). It came to be touted as an excellent pain reliever with fewer of the side effects of morphine, and it was also recommended as a safe, non-addicting substitute for morphine. Heroin, Bayer implied, was a wonder drug (although there was little evidence to support this contention), it was aggressively marketed, and it enjoyed considerable popularity in the United States where it was used for cancer, depression, cough, pneumonia, tuberculosis, and colds.[7] Some companies even marketed heroin kits that included a supply of the drug and glass syringes. However, as early as 1906, the American Medical Association was warning that heroin was very habit-forming and by 1919 there was enough bad publicity to persuade Bayer to stop making heroin. They had recently developed aspirin, it was very successful and heroin looked like a losing proposition. And with so many reports from the United States about the dangers of heroin and the formation of a new class of addicts, *junkies* (the term comes from the habit of early addicts to scrounge scarp metal and other trash – junk – to sell to support their habits) there was almost no choice.

How Opioids Work/What They Do

Opioids work in similar manner to endogenous compounds that we have in our bodies called *endorphins* (the word comes from the combination of endogenous and morphine) They bind to specific receptors in the central and peripheral nervous system. The receptors are located and distributed in a *specific pattern* and each one, when stimulated by an opioid or an endorphin, mediates specific effects. There are three *major* classes of opioid receptors (and subunits of these three) as well as several subtypes (sigma and delta) whose structure and actions when stimulated are not well understood.

The most important receptors in terms of actions of the opioids are the *Mu* (μ) receptors. There are two subtypes, μ_1 and μ_2. These are located in areas of the brain that

are concerned with analgesia, euphoria, the medullary cough center, and respiratory function, in the gastrointestinal tract, and in sensory nerve endings. Mu receptors, specifically, are involved with: [8]

μ_1 - Supraspinal analgesia, peripheral analgesia, sedation, and euphoria

μ_2 - Spinal analgesia, respiratory depression, gastrointestinal motility, bradycardia, pruritus

The *kappa* receptors are located throughout the brain, and in the spinal cord. The kappa receptors, specifically, are involved with:

κ_1 - Spinal analgesia, miosis, diuresis

κ_2 - Dysphoria, psychomimesis

κ_3 - Supraspinal analgesia

The *delta* receptors are not well understood. They appear to be involved in spinal and supraspinal analgesia. Little is known about the sigma receptors.

So the opioids work by binding to and stimulating the various opioid receptors. The actual process of binding involves *G proteins*. G proteins are linked to opioid receptors located on cell membranes. When the opioid receptor is stimulated by an opioid, the G protein initiates certain cellular effects. As the opioid receptors are inhibitory in nature, these effects might be a reduction of the cell's capacity to produce adenyl cyclase (an enzyme found inside the cell. When it is produced, it increases the formation of cyclic amp [cAMP], which in turn initiates many cellular activities, eg, opening of ion channels and cell depolarization), the chloride ion channels may open or the potassium ion channels may open (these last two actions would hyperpolarize the cell and make it more difficult for it to respond to a stimulatory impulse)[9]

Opioids then, act by binding to opioid receptors in certain parts of the brain, spinal cord and peripheral nervous system. These areas are associated with specific function, eg, respiration, analgesia, etc, and as the opioid receptors are inhibitory in nature, these specific actions are suppressed. The results are a decrease in respirations, sedation, etc.[10]

Instant feedback: The opioid receptors are inhibitory. When they are stimulated they *decrease* the activity of the tissue/organ they are located in, eg, respiratory depression

Pharmacokinetics

Opioids are well absorbed after ingestion, insufflation, and injection. They can also be inhaled (heroin is often smoked) and can be absorbed dermally (fentanyl patches are in common use for chronic pain control). The bioavailability of opioids varies: for morphine, it is reduced to 25%, for codeine, 60%. The opioids are rapidly cleared from the blood and deposited in tissues. They are metabolized by the liver and some metabolites play an active role in the effects and toxic effects of the opioid (propoxyphene and meperidine produce toxic metabolites, codeine is metabolized to morphine, morphine to a more active compound, morphine-6-glucuronide). Hepatic dysfunction can reduce the metabolism of some opioids such as propoxyphene, meperidine and pentazocine and lead to accumulation of the drug and toxic effects. Excretion is primarily through the renal route. A small amount is excreted in the gastrointestinal tract via enterohepatic recirculation.[11]

Heroin, due to its widespread abuse, deserves special mention. It is rapidly absorbed from all routes. Intravenous heroin peaks in less than 1 minute (it is very lipid-soluble and penetrates the blood brain barrier). Over the next 20-30 minutes, heroin is converted to morphine.

Important drug interactions include: [12, 13]

Meperidine/chlorpromazine: additive CNS effects
Meperidine/MAO inhibitors: Significant CNS effects, serotonin syndrome
Meperidine/cimetidine: Increased narcotic effects
Meperidine/ Phenytoin: Decreased meperidine effect
Methadone/Phenytoin: decreased methadone effect
Methadone/fluvoxamine: increased methadone effect
Morphine/cimetidine: narcotic toxicity
Dextromethorpham/MAO inhibitors: Serotonin syndrome

Pharmacologic Effects

Opioids produce the following effects: [14]

Drowsiness, and analgesia without loss of consciousness. This is mediated in the brain, spinal cord and peripherally,
Peripheral analgesia,
Miosis due to stimulation of the parasympathetic ocular nerve,
Lowered body temperature by affecting the hypothalamic heat regulation mechanism, cutaneous vasodilation, and decreased muscle activity,
Respiratory depression. The opioids have a direct effect on the respiratory centers on the brainstem. They decrease the minute volume, respiratory rate and tidal volume by altering the sensitivity of the brainstem respiratory center to carbon dioxide concentrations,
Depression of the cough reflex,

Nausea and vomiting due to stimulation of the chemoreceptor trigger zone for emesis,
Lowered blood pressure due to decreased peripheral resistance, peripheral vasodilation and inhibition of the baroreceptor reflex (Note: lowered blood pressure may also be due to the release of histamine). Also, vasoconstriction caused by increased carbon dioxide levels is blunted.
Heart rate is decreased, as is the force of contraction. The opioids increase parasympathetic activity while decreasing sympathetic activity.
Decreased gastrointestinal motility, diminished biliary and pancreatic secretion, decreased propulsive contractions of the bowel and more complete water absorption from the gut. Also, the reflex in response to rectal distension is decreased,
Inhibition of the voiding reflex and increased tone of the external sphincter,
Dilation of cutaneous blood vessels (probably due to release of histamine), and
Pruritus.

Opioids then would slow the heart rate, decrease the force of myocardial contraction and lower the blood pressure. Orthostatic hypotension is common. Respiratory rate and depth would be decreased. Body temperature would decrease. The patient would experience pain relief and be drowsy. They might feel nauseous and vomit, and urinary retention, constipation, and itching are possible.

Toxic Effects of Opioids

When they are taken in excess, the toxic effects of opioids would obviously be an extension of the normal side effects outlined above.

Respiratory depression. Opioids decrease the sensitivity of the medullary chemoreceptors to elevated blood carbon dioxide levels and also depress the response to hypoxia. Effectively, there is no stimulus for respiration. The tidal volume is a better indicator of the degree of respiratory depression than the respiratory rate. Death from opioid overdose is almost always due to respiratory depression. [15, 16]
Non-cardiogenic pulmonary edema (NCPE): This is an infrequent clinical finding in heroin overdoses (There has been speculation that the incidence is much higher, but it is not detected or detected only on autopsy. [17, 18, 19]. Also, it is almost a universal finding on fatal overdose [20, 21, 22]). The exact incidence of this complication is unclear. One author says [23] it is infrequent and estimates that it occurs in approximately 0.8-2.4% of all ED admissions for heroin OD.[24, 25, 26, 27] Earlier studies listed a much higher incidence, but there were reporting issues that made these figures suspect.[28, 29, 30] NCPE is defined as a syndrome in which the patient has hypoxia (room air saturation < 90), respiratory rate >12 and with radiographic evidence of pulmonary edema. All of this must occur within 24 hours of the overdose to be attributed to the heroin use.[31] It generally happens within minutes to hours after the overdose. The exact mechanism for this derangement is not known. Some authors have speculated it is caused by the

administration of naloxone. It is not clear if this is true or not, but this seems doubtful given the number of heroin overdoses, the amount of naloxone given and the paucity of cases of pulmonary edema in these situations. Also there are many cases of pulmonary edema being detected on autopsy on people that died of a heroin overdose but did not receive naloxone. More likely is that the pulmonary edema became evident once the coma was reversed, or a massive sympathetic outflow that occurred when the patient regained consciousness affected myocardial contractility.[32] Other authors have noted evidence of leaky pulmonary capillaries [33, 34] while others have noted that large amounts of histamine are released in heroin overdose and histamine increases capillary permeability. It is not clear which patients are at risk, but Sterret found that most patients with heroin overdose that developed pulmonary edema were "newer" users , there was a concomitant use of cocaine and/or ethanol, the Glasgow coma scale was <4, and respiratory rate was <6. [35]

Cardiovascular effects. Although opioids can lower blood pressure and cause bradycardia, these effects usually are not serious. It appears that fentanyl is most likely to cause significant hypotension while meperidine is the least likely.[36] Occasionally, however, bradycardia and hypotension can lead to ectopic activity, atrial fibrillation [37] and serious ventricular ventricular arrhythmias.[38, 39, 40] Also, profound circulatory shock) systolic blood pressure 60 mm Hg) after heroin overdose has been reported.[41]

Membrane stabilizing effect. Propoxyphene and its metabolite, norpropoxyphene, cause a blockade of the sodium ion channels in the myocardium. This produces cardiac membrane stabilization (known as the quinidine-like effect) and causes negative inotropy and QRS prolongation, and these effects are common in propoxyphene overdoses.[42] It is also important to remember that propoyxphene is usually found in combination with acetaminophen or aspirin.

Seizures: Seizures are not a common complication of opioid toxicity; when they occur, they are usually due to hypoxia, but three opioids – meperdine and propoxyphene and tramadol – are well known to cause seizures after overdose. Meperidine produces a metabolite normeperidine, and this is thought to be the cause of the seizures.[43] Seizures after tramadol – a synthetic opioid – appear to be common. Once case series[44] that reported all ingestions, intentional and accidental noted an 8% incidence of seizures while another that reported abuse and overdose cases noted an incidence of seizures of 54%.[45] As well, seizures after propoxyphene are common.[46] However, seizures have been reported, albeit rarely, after use of other opioids [47] and caution should be used when administering these drugs to the elderly or to patients with renal dysfunction.[48]

Miosis: Although not a toxic effect of opioid overdose, miosis is included here because it is an almost a certain diagnostic sign of opioid overdose.[49] Remember though, that miosis might not be seen in cases of meperidine and propoxyphene overdose, and patients with an opioid overdose may have mydriatic pupils secondary to hypoxia or coingestants.[50]

Hypothermia: This is due to decreased muscle activity, cutaneous vasodilation and an effect on the hypothalamic heat regulation mechanism. A body

temperature as low as 25 C (albeit complicated by environmental factors) has been reported.[51]

Status asthmaticus: Many heroin users who began their habits in recent years do not inject the drug; snorting or smoking is the preferred method of use. This appears to be motivated by obvious concerns for safety and avoidance of disease, but it is also motivated by the perception that insufflation and smoking are much less risky than injecting. While it is true that most fatal overdoses involve heroin injection, deaths have been reported after snorting and smoking, and there have also been some unique morbidity associated with heroin used by these routes. Status asthmaticus after snorting or inhaling heroin is not common (there are 7 reports in the literature), but many of the cases are remarkable for the degree of impairment, the need for aggressive treatment (intubation), the duration of impairment (in one cases series, the patients were intubated for an average of 5 days), and the lack of response to standard therapy. Some patients who developed status asthmaticus after insufflation or inhalational heroin use had asthma, but some did not. The link between heroin and asthma is not clear. It may simply be that heroin users are less compliant with their medication regimens, it may be a direct effect of the drug, or it may be due to a contaminant. Another possibility is that asthma produced in these circumstances is caused by the histamine release caused by opioids. [52, 53]

Wound contamination: Obviously heroin users would rarely observe aseptic technique, and there are definite risks associated with self-injection. Aside from more obvious infections, wound botulism has been reported on several occasions. [54, 55] This is particularly serious as wound botulism can produce significant morbidity, the diagnosis is difficult to make, and treatment (there is an antidote) can be delayed. Other risks of heroin injection include necrotizing fascitis.[56] Both botulism and necrotizing fascitis appear to be associated with subcutaneous injection (known as skin popping).

Toxic leukoencephalopathy: Leukoencephalopathy is the destruction of the myelin sheaths that cover nerve fibers. It is associated with neurobehavioral effects. The exact mechanism by which this disorder occurs is not clear, but it has clearly been associated with opioid use. [57, 58, 59, 60] It can be particularly devastating and lead to irreversible neurological deficits.

Neurologic deficits after smoking: One way to smoke heroin is called *chasing the dragon.* The heroin is placed on a small sheet of aluminum foil and heated. The users than inhales the vapor through a straw. Again, many users consider this a safe way to use heroin, but there has been a report of reversible parkinsonism after heroin inhalation.[61] Also, several authors have noted severe abnormalities of the magnetic resonance imaging studies and the computed tomography studies after heroin inhalation.[62, 63, 64]

Rhabdomyolysis and renal failure: Rhabdomyolysis occurs when there is injury to muscle and the myocyte contents leak into the plasma; it is a common cause of renal failure. It has been reported infrequently after heroin use, both after injection and after smoking.[65, 66] The exact cause is not know: direct toxic effects of the drug, allergies, prolonged compression (heroin users may lie immobile for several hours after using the drug), decreased food and fluid intake, adulterants

(quinine) and vascular occlusion are possible causes. [67] Not surprisingly, renal failure secondary to rhabdomyolysis has been reported. [68]

Contaminants: Heroin is frequently adulterated with a variety of substances in order to increase the bulk and increase profits, and at times this has produced unusual toxic presentations. During 1995 and 1996, health departments and emergency rooms reported 325 cases (and there were certainly more that weren't reported) of heroin being adulterated with scopolamine. The patients presented in the field with the traditional clinical picture of opioid toxicity, ie, coma and respiratory depression. However, when naloxone was administered, the patients became agitated, confused, hypertensive and tachycardic. Some of these effects may be seen in patients who have had opioid toxicity reversed with naloxone, but in these patients, the effects were pronounced and prolonged, and accompanied by other signs of anticholinergic poisoning. This presented ED personnel with a series of cases that were very confusing. Eventually, laboratory analysis of street samples revealed the presence of scopolamine.[69] And in early 2006, heroin in Philadelphia and New York was adulterated with fentanyl. Patients who had overdosed presented to emergency rooms with a typical clinical picture of opioid poisoning, but did not respond to standard doses of naloxone.

The list of toxic effects associated with the opioids is long and complex, but the clinical picture of the vast majority of patients who present with opioid intoxication is predominated by *central nervous system depression, respiratory depression and miosis*. Patients presenting with these signs are almost certainly under the influence of an opioid. There are other drugs that can produce similar effects, eg, clonidine, phenothiazines, some of the sedative-hypnotics, yet with a skilled and careful assessment, it is possible to distinguish the patient with a true opioid overdose.

Instant feedback: Coma, respiratory depression and miosis; these are the hallmarks of an opioid overdose.

Fatal exposures

Most fatal exposures to opioids are due to heroin, and the great majority of those occurred when the drug was used intravenously, although deaths have been reported by intranasal and oral use. [70, 71] Many people who succumb are experienced users. Multiple drug use is common – alcohol and benzodiazpines are common coingestants. Oddly, the blood levels of morphine found in patients with fatal overdoses is often no higher than what has been measured in survivors. A loss of tolerance has been advanced as a cause and there is a trend that shows fatal overdoses occur after a period of abstinence.

Morbidity associated with heroin use

Heroin users are susceptible to a wide range of morbidity. The drug depresses the sensorium and decision-making and concentrated action suffer. Nausea and vomiting are common. On a long-term basis, heroin users may develop infectious diseases such as hepatitis B and C, HIV/AIDS, bacterial infections, cardiomyopathy and valve infection, collapsed veins and skin abscesses. They also run the risk of addiction and physical dependence.[72]

Body packers/body stuffers

Swallowing heroin packages to avoid arrest (body stuffers) or in an effort to smuggle the drug across borders (body packers) is a common occurrence. Depending on the situation, the patient may pass these packages uneventfully (as is often the case with body packers; the packages are often very well sealed) or they may suffer severe toxicity (far more likely with body stuffers, as these packages are not tightly sealed and are swallowed hurriedly). Management of these cases is simple, but difficult for both the patient and the nursing staff. The number and location of the packages should be confirmed by x-ray. If the x-ray is negative but there is a strong suspicion that the patient has swallowed drug packages, CT or MRI can be used. If the patient is a stuffer, administer a dose of activated charcoal. Follow that with an infusion of whole bowel irrigation (more on this in a later section), a solution that will mechanically remove the packages from the bowel. If the patient is a body packer, charcoal can be given, but it is probably more effective to start whole bowel irrigation. In either circumstance, these patients need very close monitoring. The amount of drug that is swallowed in these circumstances is usually far beyond the normal dose and is frequently a lethal amount. [73] Rarely, if the packages are not removed by whole bowel irrigation, surgery may be needed. Endoscopy can be attempted, but this poses the risk of rupturing the packages during removal. [74, 75]

Heroin and cocaine: the speedball

Heroin users will, at times, use both their habitual drug and other drugs, and the combination of heroin and cocaine is called a *speedball*. Users report that taking the two together produces a more pleasurable high, and heroin can help to ameliorate uncomfortable sympathomimetic effects of cocaine.

This combination has long been considered to be particularly dangerous, but there is actually very little in the medical literature to support this contention. Much of the literature focuses on the effect on patterns of use of either drug when they are used together and the particular risks, eg infection, that are common to all IV drug users. There are a few reports of acute human exposure [76, 77] and animal experiments have not been uncommon, but despite this attention, there is little definite known about the interaction between the two drugs or the specific physical dangers of a speedball.[78]

Treatment of opioid overdose

Treatment of an opioid overdose should focus on (1) maintaining a patent airway, (2) making sure the patient is adequately oxygenated, (3) supporting the pulse and blood pressure, and (4) monitoring for complications. It is best to use an ordered approach that reflects these treatment goals.

Therapy for a patient with an opioid overdose should always start with assessment and stabilization of the airway, breathing and circulation – the ABCs. A rapid assessment should be made of the rate and depth of the patient's respirations and the oxygenation status. Supplemental oxygen should be administered; the exact method of delivery will depend on the status of the patient's consciousness and the adequacy of respirations. Hypotension can be treated with fluids, trendelenburg position and IV vasopressors. Bradycardia is seldom severe enough to require intervention, but if the patient's hemodynamic status were compromised because of a slow heart rate, atropine would be the drug of choice.

Once the ABCs have been stabilized, consider gastric decontamination. Decontamination is the term used for efforts to prevent the absorption of a toxin or to remove a toxin from the gut. There are four methods: (1) Syrup of ipecac. This syrup acts locally in the gut and centrally in the brain to produce emesis. It is most effective if it is given within 30 minutes of ingestion, and the vomiting it produces can last for four hours. Due to the potential for CNS depression and loss of gag reflex in the patient with an opioid overdose, ipecac should *never* be used in these situations, (2) Lavage. This method of decontamination makes intuitive sense; if the patient has ingested a poison, put a tube into their gut and suck it out. Studies have shown that to be effective it must be performed within an hour of an ingestion. Situations in which lavage would be appropriate for an opioid overdose would be rare, (3) Whole bowel irrigation. This technique instills a large amount (1-2 liters per hour) of isotonic fluid into the gut to mechanically remove any toxin that remains in the stomach or intestines. Again, situations in which whole bowel irrigation would be appropriate for an opioid overdose (except for body packers and stuffers) would be very unusual, and (4) activated charcoal. Activated charcoal adsorbs drug that is in the stomach and intestine, but it is only useful if it is used within a few hours of an ingestion. Given the fact that almost all opioid overdoses involve injection, insufflation or inhaling, gastric decontamination would rarely be indicated. Instead, unlike many overdoses, gastric decontamination would be a secondary consideration and with an opioid overdose, after the ABCs have been stabilized, the next step is to administer the antidote for opioid overdose, naloxone.

Naloxone

Naloxone is a specific antidote for opioid poisoning (Note: There have been anecdotal reports of naloxone reversing the central nervous system depression caused by ethanol, benzodiazepines and other drugs, and naloxone has been used to treat septic shock and stroke victims, but there is no conclusive evidence that clearly supports its use for anything beyond opioid exposure). Naloxone is a derivative of oxymorphone and it is a competitive antagonist at the mu opioid receptors. It also has a lesser effect on the kappa receptors and the delta receptors. Naloxone binds to the opioid receptors and prevents opioids from binding to them and it (essentially) produces no pharmacological action of its own. Given that it binds preferentially to the mu receptors, it will effectively reduce central nervous system depression, respiratory depression, and bradycardia caused by an opioid. Naloxone will not reverse the sodium channel blockade seen in propoxyphene overdose or the mast cell release of histamine, and for certain drugs such as pentazocine in which there is little mu receptor binding, naloxone may be less successful at reversing toxic effects. Seizures caused by opioids can be treated with naloxone, but if the patient has taken meperidine or tramadol and is seizing, naloxone may not be effective. It has a duration of action of approximately 20-90 minutes. The onset of action and duration of action would be longer when the drug is given IM or SC.

To use naloxone correctly, it is best to use this approach:

> Indications: Naloxone should be given to patients who have ingested a toxic amount of an opioid and who have evidence of respiratory compromise. *The primary goal of administering naloxone is to ensure adequate oxygenation, not to restore the patient to full consciousness.* Restoring the patient to full consciousness can be very uncomfortable to the patient (agitation, diaphoresis, headache, tachycardia, tremor, nausea, and vomiting) and potentially dangerous to the staff (confused and/or aggressive behavior by the patient.[79]
> Contraindications: There are essentially none, except the need to avoid using naloxone to restore full consciousness.
> Adverse effects: Naloxone is a very safe drug, In human volunteers, excessively high doses produced very few minor, or more often no, side effects.[80] However, over the years there have been scattered case reports of serious complications following naloxone administration. *Pulmonary edema:* In a case series of 453 patients with heroin overdose, one patient developed pulmonary edema (as seen on x-ray) after naloxone;[81] a young, healthy postoperative patient developed pulmonary edema after being given 2 doses of naloxone; a 70-year-old male with a history of congestive heart failure underwent coronary artery bypass surgery, Postoperatively he was given naloxone and developed clinical (but not radiographic) signs of pulmonary edema.[82] There have been other reports in the literature of pulmonary edema following naloxone administration, but many of them shared the limitations of the studies mentioned, ie, the pulmonary edema was not confirmed by x-ray, it occurred after heroin overdose, it occurred in postoperative patients with a history of heart disease, or the clinical findings were suggestive, but not definitive, for pulmonary edema. As enormous doses have been well tolerated and naloxone has been in widespread use for many years,

most case reports (that have limitations) that purport to establish a link between naloxone and pulmonary edema must be view cautiously. However, there have been several well documented cases of pulmonary edema after naloxone administration.[83] The conclusion? If pulmonary edema is an adverse effect of naloxone, it is rare; *Asystole/ventricular irritability:* Several cases of asystole [84], [85] and ventricular fibrillation [86, 87] have been reported. The cases were complicated in some instances by coingestion of cocaine and heroin, and severe heart disease. It is not entirely clear there was a causal relationship, and the mechanism of action is not clear; it is possible that reversal of opioid intoxication caused a massive catecholamine surge; *Hypertension:* There have been numerous reports about hypertension after naloxone administration.[88, 89, 90] As with many of the cases of pulmonary edema following naloxone administration, in some of these cases there have been confounding factors. But unlike most of the cases of pulmonary edema, some of these cases of hypertension, although unusual, seem to be directly related to naloxone. It has been speculated that hypertension after naloxone use is precipitated by a catechoamine surge.[91] It is also possible that the endogenous opioids play a role in controlling blood pressure; beta-endorphins may lower blood pressure, thus administering naloxone would cause hypertension;[92] *Gastrointestinal effects*: nausea and vomiting are common side effects of naloxone. Agitation and confusion are common and these can be dangerous to the staff and the patient.

Dose: Depending on the source, the recommended dose of naloxone varies. A standard dose is often listed as 0.4-2 mg as an IV bolus, and a similar dose for children. This dose can be repeated at 2 to 3 minute intervals until a total of 10 mg has been reached (the upper limit is not so much a *dosing* limit as it is a clinical fact that in *most* circumstances, if a patient has not responded in some way to 10 mg of naloxone, they are not opioid-toxic.) However, other sources note that 0.4 mg is an amount that will produce withdrawal in an opioid-dependent patient, and 0.05 mg IV is recommended, followed by doses of 0.4 and 2 mg. The ideal dose would be titrated according to the amount of drug taken, the drug taken, and the number and type of opioid receptors that have been occupied, but these are facts that would not be available. The best recommendation would be to start with the lowest dose that will reverse respiratory depression and that avoids withdrawal.

Instant feedback: Coma, of course, carries its own risks, *but patients who succumb to toxic doses of heroin die because or respiratory depression, not because they are in a coma.* Remember: the goal of treatment with naloxone is *not* reversal of coma and full consciousness; it is to restore and maintain adequate respirations and ensure oxygenation.

Instant feedback: Most opioid overdoses will respond in some way to a dose of up to 10 mg of naloxone, but there are exceptions. Naloxone has its greatest effects on the mu receptors and propoxyphene and pentazocine bind more closely with the kappa and delta receptors. Overdoses with these drugs may require greater than normal amounts of

naloxone.[93] Also, oxycodone (which is a very strong narcotic that is often a sustained release product) and fentanyl (also a strong narcotic) may also be refractory to large doses of naloxone.[94]

Instant feedback: To avoid giving frequent doses of naloxone, consider using a naloxone drip. The standard formula is to deliver, each hour, ⅔ of the dose that was successful in restoring normal respiratory status. Example. The patient required 6 mg of naloxone, so the goal is to deliver 4 mg an hour. Put 40 mg of naloxone in a liter of fluid and infuse it at 100 cc per hour.

> Route: Naloxone can be give IV, SC, IM, orally, endotracheally, intralingually, intranasally, enterally, transdermally, sublingually and via nebulization and all of these routes – for their particular purpose – have proven successful. Obviously for instances of acute opioid overdose, the parenteral routes are preferred. Traditionally in the situation of a symptomatic overdose, naloxone has been given IV. Occasionally, the IM or SC routes can be used to prolong the effect, but the onset of action will be slower than the IV route.

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