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Opioid Toxicity

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-When considering overdoses of opioids (narcotics), **heroin** (diacetylmorphine) is probably the first drug that comes to mind, and we picture users as long-term habitual drug abusers of low socioeconomic status. This association is actually unjustified, since victims of opioid overdose may be any age and represent all social and economic levels, and the drug may be obtained by illicit means or legally obtained by prescription.

-Drugs of concern include: Morphine , Methylmorphine (Codeine), Hydrocodone (dihydrocodienone), Oxycodone ,Oxymorphone ,Hydromorphone, Diacetylmorphine (heroin), and others.

-The natural opium alkaloids have been used for centuries. The familiar dried exudate of the un-ripened seed pod of the Asian poppy plant, *Papaver somniferum*, contains at least 25 different alkaloids. The phenanthrene derivatives, morphine and codeine, are the two major naturally occurring opioids.

-It has been postulated that toxic effects are related to different actions of these drugs at various opiate receptors in the CNS . A listing of some opioids and their associated receptor sites is shown in Table 13.2. Clinical responses of analgesia , euphoria , respiratory depression, and miosis are believed to result from occupation of the μ-receptors. Different type of analgesia results when the *k*-receptors are involved, and the psychogenic effects, such as dysphoria, delusions, and hallucinations, result from opioid action at the δ-receptors.

TABLE 13.2. *Opioid receptors for possible toxic action*

Receptor	Opioid	Clinical effect
mu	Morphine-like analgesics	Analgesia Euphoria Respiratory depression Miosis
kappa	Pentazocine Nalorphine Cyclazocine (morphine-like analgesics may have some kappa activity) Levallorphan	Analgesia Sedation Miosis
sigma	Pentazocine Cyclazocine Nalorphine	Dysphoria Delusions Hallucinations

-Acute opioid toxicity may result from a variety of situations. These include intentional, accidental, or therapeutic overdose of prescribed medications. Whatever the reason, the toxicologic effects are basically the same. The most common characteristics of acute opioid toxicity are listed in Table (**13.3**) below:

Table 13.3. Characteristics Of Opioid Toxicity

-CNS* depression-coma
-Respiratory depression
-Pulmonary edema
-Hypothermia
-Miosis
-Bradycardia
-Hypotension
-Decreased urinary output
-Decreased gastrointestinal motility

-Signs and symptoms associated with acute opioid overdose usually begin within 20 to 30 min after oral ingestion and within minutes after parenteral administration. The most significant effects involve opioid action on the CNS. Nausea and vomiting are also among the first **symptoms noted**. Vomiting results from stimulation of the chemoreceptor trigger zone (CTZ) and is less likely to occur if the victim is kept in the recumbent position.

-The most obvious and severe toxic effect of opioid poisoning **is central depression**. The victim is usually asleep or in a stuporous condition. The extent of CNS depression and its duration will vary according to the opioid involved, the quantity, and route of administration. For a large overdose, the victim rapidly lapses into coma and is not arousable by verbal or painful stimuli.
-In acute overdose, respiration will be severely depressed to a rate as low as 2 to 4 per min. Cyanosis becomes apparent and many victims have a frothy pulmonary edema. In humans, death from an acute opioid overdose is almost always from respiratory arrest. When there is high concentration of drug in the medulla and brainstem, there is decreased sensitivity of the brainstem respiratory centers to increases in carbon dioxide, and, in the medulla, there is depression of the rhythm of respiration.

- **Respiratory depression** with acute overdose is further complicated by bradycardia and hypotension. There are two possible explanations for the decrease in heart rate. One theory suggests that **opioids stimulate the vagal centers**. The other suggests that there is selective depression of the supra-medullary centers which can lead to suppression of autonomic reflexes. During acute poisoning, blood pressure is normally not greatly affected. Hypotension usually occurs in the later stages of poisoning and results from hypoxia.

-**Pinpoint pupils (miosis)** are usually considered to be the classical sign of narcotic poisoning. Tolerance to miosis does not occur. In some overdoses, however, the pupils may not be constricted, due to asphyxial changes resulting from decreased pulmonary oxygen exchange. Therefore, the pupils relax and dilate. When mydriasis occurs, the victim's prognosis is grave.

-The body temperature usually decreases and the skin feels cold and clammy. This is due to suppression of the hypothalamic heat regulatory mechanisms. Skeletal muscles also become flaccid and sometimes the jaw relaxes. The tongue may even fall back to block the airway. There is decreased urinary output, which can be related to release of antidiuretic hormone (ADH).

-**Gastric motility and tone of both small and large intestines may be decreased**, resulting in severe constipation. In the case of massive overdose, convulsions may occur due to stimulation of the cortex. Death, even in an addict, is almost always due to respiratory failure, complicated by such factors as pneumonia, shock, and pulmonary edema. The usual triad of coma, pinpoint pupils, and depressed respiration strongly suggests an opioid overdose, but accurate diagnosis also depends on the individual's history and evidence of prior drug misuse.

-Management of Opioid Toxicity:

Opioid ingestions frequently delay gastric emptying. Thus, in acute overdose, as long as the patient is alert, emesis should be performed. If the patient is obtunded, gastric lavage is indicated.

-Since victims of opioid overdoses are often comatose with depressed respiration, the major treatment objective is to support and maintain vital functions. Therefore, the first step is to provide adequate respiratory assistance and cardiovascular support.

- Opioid overdoses are treated readily with an **ideal direct antagonist**. The use of an antagonist brings about dramatic improvement in respiration within minutes. Overall, the antagonist will reverse CNS depressant, analgesic, convulsant, psychotogenic, and dysphoric actions of opioids.

-Levallorphan is an opioid antagonist, but it has partial agonist action. Major disadvantages to its use are with semi-comatose or comatose individuals, in whom CNS depression is not due to an opioid, or in whom depression is partially due to some other CNS depressant, **such as alcohol or barbiturates. In these cases ,** the partial agonistic activity may produce additive depressant effects. Mixed poisonings are common. For this reason, a pure antagonist is preferred.

-Naloxone was the first pure opioid antagonist, and it is considered the drug of choice for treatment of opioid intoxications. Dramatic improvement in respiration is seen within minutes after it is administered. Its purity as an antagonist, though, has been challenged. Limited data indicate that it may also possess some degree of agonist activity.

The recommended initial dose of naloxone is 0.4 mg for adults and 0.01 mg/kg for children. Several doses may be given at 2- to 3min intervals. If CNS depression is due to an opioid, coma and respiratory depression will be resolved with 1 to 2 min. If it is not due to an opioid, naloxone will not worsen the existing condition. Since it has a short half-life of 60 to 90 min, and usually causes no ill effects in a patient without an opiate overdose, a 2-mg bolus may be given and, if necessary, repeated within 5 min. Twenty to 24 mg may be required for severe opioid intoxication.

Table **13.4** lists half-lives of representative opioids. It should be noted that for substances with long half-lives, larger doses of naloxone are

frequently required. For example, acute oral ingestions of a toxic dose of a long-acting opioid, such as methadone or propoxyphene, will be managed better by continuous infusion of naloxone rather than by bolus administration . The reason for continuous infusion is based on the fact that respiratory depression may recur because of naloxone's short half-life.

TABLE 13.4. *Comparison of opioids*

Narcotic	Equianalgesic dose (mg)	Blood concentrations: Plasma half-life (hr)	Therapeutic (μg/dL)	Toxic (μg/dL)	Lethal
Morphine	10	2.5–3	1–7	10–100	>400 μg/dL
Codeine	120	3–4	1–12	20–50	>60 μg/dL
Heroin	3–4	2.5–3	—	10–100	>400 μg/dL
Methadone	8–10	15 single dose 22–25 maintenance	30–100	200	>400 μg/dL
Propoxyphene	240	about 12	5–20	30–60	80–200 μg/dL
Meperidine	80–100	3–4	30–100	500	1–3 mg/dL
Pentazocine	30–50	2–3	10–60	200–300	1–2 mg/dL
Hydromorphone	1.5	2–4	0.1–3	10–200	>300 μg/dL
Oxycodone	15	—	1–10	20–500	—

-Comatose patients must be aroused as quickly as possible. If hypoxia persists and adequate tissue oxygenation is not achieved quickly, capillary damage followed by shock is likely to ensue. Patients with pulmonary edema are at special risk. Diuretics, digitalis, steroids, and antihistamines have all been recommended as supportive therapy. However, all have doubtful efficacy.

- Respiratory depression lasts much longer than the antagonistic effects o f naloxone. The patient must, therefore, be closely monitored for at least the next 24 to 48 hr. If depressed respiration reappears, additional naloxone is necessary. Naloxone should ideally be used only to return respiration to normal. Other symptoms can usually be managed by other means. A victim of overdose who is breathing normally does not need naloxone.

-Naturally Occurring Opioids:

''Codeine''

Codeine, or methylmorphine , possesses analgesic and antitussive properties. It is less potent than morphine, i.e., 120 mg of codeine produces the same degree of analgesia as 10 mg of morphine. Also, tolerance does not develop as rapidly with codeine compared to morphine. Toxicity and death due to codeine alone are infrequently encountered. The lethal dose is between 500 mg and 1 g. Acute toxic ingestions of codeine produce the typical triad of symptoms seen with morphine; coma, miosis, and respiratory depression. Codeine is usually taken in combination with other drugs, including analgesics, antihistamines, expectorants, or sedatives. When ingested concurrently with other agents, the toxic dose is lower . Besides the legitimate

pharmaceutical preparations available, users of illicit preparations have also found that the combination of codeine with glutethimide taken orally may produce euphoria comparable to heroin, lasting about 6 to 8 hrs.

-Synthetic Opioids:

''Diphenoxylate''

Diphenoxylate is a meperidine congener used in combination with atropine in an antidiarrheal preparation (**Lomotil, EnteroStop**). The therapeutic dose is 20 mg daily (adults), and 3 to 10 mg daily (children). Despite the fact that diphenoxylate is not indicated for children under age 2, accidental and therapeutic intoxications are a problem. Unfortunately, most people do not view diphenoxylate products as extremely toxic, so they leave them carelessly unattended on bedroom tables or elsewhere where children have easy access to them. There is an extremely narrow dose range between therapeutic and toxic blood concentrations (Therapeutic Index) in children. Although part of the toxicity problem with diphenoxylate products in children is due to the opioid component, a large portion is due to the anticholinergic activity of atropine.

-Acute intoxications, especially in children, are characterized primarily by anticholinergic effects. These may consist of hyperpyrexia, flushing of the skin, lethargy, hallucinations, urinary retention, and tachycardia. This phase is followed by miosis, respiratory depression, and coma due to the opioid activity. Symptoms are highly variable and dose dependent. The quantity of atropine contained in each Lomotil dose is sub-therapeutic, although it will cause anticholinergic side effects, and these are magnified when taken in overdose.

''Fentanyl (Sublimaze)''

This is a synthetic opioid agonist that was initially introduced for short-term use as an anesthetic . As a prototype for this category of opioids, other fentanyl derivatives have been synthesized for medicinal uses; all have a much greater analgesic action than morphine. One derivative, 3-methylfentanyl, has been responsible for more than 100 overdose deaths in California alone since 1979, and in one county in Pennsylvania more recently**.**

Several fentanyl derivatives have surfaced on the illicit market as *''designer drugs''*. The term applies to synthetically modified controlled substances, such as fentanyl, meperidine, or amphetamine, using commonly available industrial chemicals in the manufacturing process to avoid the Federal Controlled Substances Act. Therefore, these drugs were temporarily *legal* . Alpha-methylfentanyl is 200 times as potent as morphine, and the minimum lethal dose is about 125 µg. 3-Methylfentanyl is 7,000 times as potent as morphine, and the minimum lethal dose is reported at 5 *µg.*

As with other opioids, the most significant acute toxic effect of fentanyl derivatives is **respiratory depression**, which is dose-dependent and may last up to 30 min. The hemodynamic effects include bradycardia and hypotension. The remaining characteristics of toxicity include chest wall rigidity, nausea, vomiting, hypothermia, and seizures.

''Meperidine''

Meperidine hydrochloride (Demerol) is a **pure opioid agonist that was described initially** in 1939 as an anticholinergic drug. It was the first synthetic opioid to be marketed.

It is one of the most commonly used opioid analgesics. Its structure is dissimilar to morphine, but similar to fentanyl. Like other opioids, meperidine exerts pharmacodynamics actions by binding to opioid receptors, particularly the K-receptor. A 75 to 100 mg dose of meperidine, given parenterally, will produce an equianalgesic response to 10 mg morphine.

-Since **meperidine undergoes first-pass metabolism**, oral administration produces less than **one-half the total analgesic response** compared to parenteral administration. When meperidine is prescribed for postoperative or chronic pain, it is often **necessary to increase the dose** to maintain the therapeutic response. However, a potential problem may result from cumulative doses of meperidine.

Meperidine is metabolized in the liver by two pathways . The first involves **hydrolysis** by carboxyesterase to meperidinic acid. **The other involves N-demethylation by microsomal enzymes to normeperidine, an active metabolite**. Elimination half-lives for meperidine and normeperidine are 3 to 6 hrs. and 24 to 48 hrs., respectively. Since normeperidine has a longer $t_{1/2}$, repeated administration of meperidine will result in elevated normeperidine/meperidine ratios.

Normeperidine has been shown to have **one-half the analgesic activity**, but two times the convulsant activity of meperidine. When meperidine is administered orally, the normeperidine/meperidine ratio is higher, compared to parenteral administration. This is related to the high first-pass effect, also.

Normeperidine concentration also accumulates with impaired renal function and in cancer patients. Neurotoxicity of normeperidine is manifest by signs of CNS stimulation, including tremors, twitching, multifocal myoclonus and seizures. These signs can be correlated directly to **normeperidine concentrations**, and generally appear after several days of meperidine use .Unfortunately , normeperidine toxicity is often unrecognized, but should be considered in patients receiving large doses of meperidine.

Treatment of normeperidine toxicity consists of **discontinuing use of meperidine** and giving a benzodiazepine derivative to reduce CNS excitation. Naloxone should be given carefully, if at all, because it may increase the incidence of seizures .Normeperidine toxicity may be prevented by avoiding prolonged administration of meperidine, especially in patients with impaired renal function.

A meperidine analog, l-methyl-4-phenyl- 1,2,5,6-tetrahydropyridine (MPTP) has appeared on the street among intravenous drug abusers. It was sold as a new synthetic heroin. Use of MPTP has been associated with a severe form of parkinsonism . It has been shown to cause selective destruction of the substantia nigra . All patients responded to therapy with a combination of L-dopa and caibidopa (Sinamet).

''Pentazocine''

Pentazocine (a benzomorphan derivative) that is 3 to 4 times less potent than morphine as an analgesic, Its illicit use has continued to increase over the years.

A Pentazocine exerts its major actions on the CNS and smooth muscles. CNS effects include analgesia, sedation, and respiratory depression at doses of 20 to 30 mg. Parenteral doses of 60 to 90 mg may produce psychiatric disturbances, including dysphoria, depression, confusion, and hallucinations .

The cardiovascular responses to pentazocine differ from other opioids in that high doses cause increased blood pressure and heart rate, flushing, chilis, and sweating. These effects may occur because pentazocine increases blood concentrations of epinephrine and norepinephrine . Both tolerance and physical dependence have been reported with frequent and repeated use of pentazocine.

''Propoxyphene''

Propoxyphene (dextropropoxyphene) is a synthetic analog of methadone, and, if taken in overdose, causes all the classic signs of opioid poisoning. Both the hydrochloride and napsylate salts cause similar toxic problems. As with diphenoxylate containing products, most people do not consider the toxic potential of propoxyphene to be great. Too frequently, large quantities are being used for trivial pain without advising the recipient of the potential for toxicity.

One special concern is ingestion of a product that also contains acetaminophen . Clinical symptoms caused by propoxyphene overdose may completely overshadow those of a toxic acetaminophen ingestion. The problem is magnified when the victim has previously taken ethanol, a barbiturate, or other CNS depressants, as is frequently the case . These agents stimulate the hepatic mixed-function oxidase enzymes responsible for converting acetaminophen to its toxic intermediate metabolite. They also potentiate the CNS sedative action of propoxyphene. The influence that ethanol exerts on propoxyphene toxicity, as shown by blood concentrations of propoxyphene at the time of death.