Robert H. Williams, PhD, DABCC, MT(ASCP)
Timothy Erickson, MD

Emergency Diagnosis of Opioid Intoxication

ABSTRACT *Opioids are widely used for analgesic purposes. If taken as prescribed, they are safe and effective. Overdosing, however, can cause coma and life-threatening respiratory depression. In the acute care setting, physicians often base treatment on the presence of classic "opioid syndrome" characteristics—mental status depression, hypoventilation, miosis (pinpoint pupils), and reduced bowel motility. Rather than identify and quantify the specific agent, laboratories should confirm opioid intoxication qualitatively with a urine drug screen. With this information, physicians may expedite treatment with opioid antagonists (naloxone), which help patients to resume spontaneous respiration. Because the drug level does not always correlate with the severity of illness, quantitative drug levels are rarely needed. Hypoglycemia, hypoxia, and hypothermia are also seen with opioid overdose.*

This is the first article in a 3-part continuing education series on drugs of abuse. On completion of this article the reader will be able to correlate clinical findings with laboratory data to assist the clinician in diagnosis and describe therapeutic interventions for managing patients with opioid poisoning.

From the University of Illinois at Chicago Medical Center, Departments of Pathology (Dr Williams) and Emergency Medicine (Dr Erickson), Chicago, IL.

Reprint requests to Dr Williams, University of Illinois at Chicago Medical Center, Department of Pathology, Division of Clinical Pathology (M/C 750), 840 S Wood St, 201G CSB, Chicago, IL 60612; e-mail: rwilliam@uic.edu

Case Presentation

A 25-year-old man with a history of drug abuse was unresponsive to treatment by paramedics at an inner-city nightclub. On arrival to the emergency department, the patient was hypoventilating, cyanotic with small pupils, and responding only to deep painful stimuli. The patient's skin was cool and dry. Needle tracks were observed along the upper extremities. His pulse was 56 beats per minute; respiration rate, 6 per minute; blood pressure, 95/60 mm Hg, and temperature, 35.4°C (95.8°F). The patient's abdomen was soft and had hypoactive bowel sounds. An electrocardiogram revealed a sinus bradycardia.

Suspecting opioid overdose, the physician ordered tests (Table 1) and intravenously administered a bolus dose of 0.4 mg of naloxone and 50% dextrose. Although the patient began to arouse from coma within a few seconds, he quickly relapsed into respiratory depression. The physician gave a higher (2 mg) bolus dose of naloxone. The patient responded within 1 to 2 minutes and became fully alert and oriented, and his pupils became dilated. He was also diaphoretic and appeared agitated. Lung examination showed bilateral rales auscultated at the bases. A chest radiograph revealed diffuse patchy infiltrates. The classic symptoms of opioid overdose coupled with the opioid-positive urine drug screen test result confirmed the diagnosis of opioid intoxication.

The patient was given 50% dextrose for his hypoglycemia. Because he had a history of drug abuse, the patient was kept an additional 8 hours for observation and psychiatric evaluation for drug-abuse detoxification. Although admitting to frequent heroin abuse, the patient denied suicidal attempts and claimed he "just had a bad cut tonight." He remained in the emergency department for several hours, became more uncooperative, and demanded to be discharged.

History of Opioids

The medicinal value of opiates has been known for more than 2,000 years.[1] The naturally occurring alkaloid analgesics come from the poppy plant, *Papaver somniferum*. The milky exudate from unripe seeds of this plant contains several pharmacologically active compounds such as

Downloaded from https://academic.oup.com/labmed/article/31/6/334/2657111 by guest on 21 August 2022

Table 1. Laboratory Test Results for Patient Suspected of Opioid Intoxication

Test	Result	Reference Range
Arterial blood gas levels: room air/40% oxygen		
pH	7.20/7.39	7.35-7.45
pCO_2, mm Hg	60/37	35-45
pO_2, mm Hg	50/135	90-95*
Bicarbonate, mmol/L	18/22	24-28
Serum constituent levels		
Electrolytes		
Sodium, mEq/L (mmol/L)	145 (145)	136-145 (136-145)
Potassium, mEq/L (mmol/L)	3.2 (3.2)	3.5-5.0 (3.5-5.0)
Chloride, mEq/L (mmol/L)	109 (109)	99-109 (99-109)
Bicarbonate, mEq/L (mmol/L)	18 (18)	22-28 (22-28)
Urea nitrogen, μmol/L (mg/dL)	29 (10.4)	10-20 (3.6-7.1)
Creatinine, μmol/L (mg/dL)	1.2 (106)	0.6-1.2 (53-106)
Glucose, mmol/L (mg/dL)		
Before 50% dextrose	55 (3.1)	70-105 (3.9–5.8)
After 50% dextrose	125 (6.9)	70-105 (3.9–5.8)
CBC		
RBC count, $\times 10^6/\mu L$ ($\times 10^{12}/L$)	3.9 (3.9)	4.7-6.1 (4.7-6.1)
WBC count, /μL ($\times 10^9/L$)	9,500 (9.5)	4,800-10,800 (4.8-10.8)
Hemoglobin level, g/dL (g/L)	12.0 (120)	14.0-18.0 (140-180)
Hematocrit, % (proportion of 1.0)	37 (0.37)	42-52 (0.42-0.52)
Platelet count, $\times 10^3/\mu L$ ($\times 10^9/L$)	120 (120)	150-400 (150-400)
Blood ethanol level, mg/dL (mmol/L)	70 (15.2)	<5 (<1.1)
Drugs in urine		
Amphetamines	None detected	None detected
Cannabinoids	None detected	None detected
Cocaine metabolite	None detected	None detected
Barbiturates	None detected	None detected
Opiates	Positive	None detected
Phencyclidine	None detected	None detected

*Room air.

morphine and codeine (methylmorphine). The dried extract is "opium." Although morphine (named after Morpheus, the god of dreams) is the principal alkaloid of opium, "opioid" refers to the naturally occurring compounds, semisynthetic alkaloids prepared from the extract, and synthetic surrogates with morphine-like pharmacologic effects (rather than morphine-like structures).[2]

In 1874, heroin (diacetylmorphine) appeared as the first semisynthetic derivative made from morphine. It became available as a pharmaceutical preparation in 1898. Although therapeutic use of heroin is illegal in the United States, it rose to epidemic proportions by the 1970s (Fig 1). In response to increasing concerns about opioid addiction and toxicity, Congress made the nonmedicinal use of opioids illegal by passing the Harrison Narcotic Act in 1914. Today, with lower

Downloaded from https://academic.oup.com/labmed/article/31/6/334/2657111 by guest on 21 August 2022

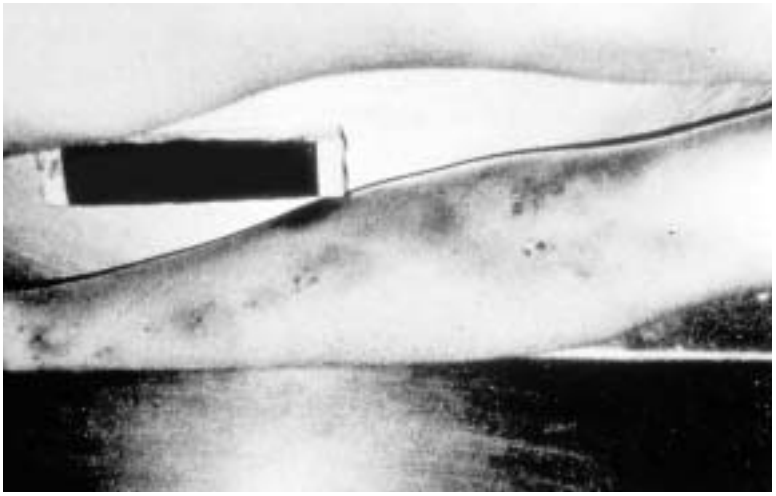


Fig 1. Needle tracks are evident on the arm of a man who was found dead due to an apparent heroin overdose.

Table 2. Opioid Receptors and Their Clinical Effects

Receptor	Clinical Manifestations
Mu	Analgesia
	Spinal (mu_2)
	Supraspinal, brain (mu_1)
	Central depression
	Bradycardia
	Hypothermia
	Reduced gastrointestinal tract motility
	Respiratory depression
	Miosis (ie, pupil contraction)
	Physical dependence
	Pruritis (ie, itching)
Kappa	Miosis
	Sedation
	Spinal analgesia
Delta	Delusions
	Dysphoria (ie, restlessness or malaise)
	Hallucinations
	Psychomotor change

prices and higher purity, heroin is a prevalent street drug.[3] Users claim that it gives an enhanced euphoric effect. Because intravenous injections have led to complications such as endocarditis and AIDS, abusers have sought other, less risky modes (intranasal, smoking) of administration. Although traditionally smuggled from Southeast Asia, Afghanistan, and Nigeria, most heroin in the United States comes from South America and Mexico.

Opioid Metabolism and Pharmacology

Most opioids are readily absorbed after injection. Absorption is also high from the gastrointestinal tract, although bioavailability and pharmacologic effects vary with rates of first-pass metabolism. Protein binding of opioids in plasma varies considerably, and tissue localization depends on lipid solubility and tissue perfusion. Metabolism takes place primarily in the liver. Because some opioids undergo significant first-pass metabolism, giving the drug orally may reduce its efficacy. Metabolites are excreted primarily in the urine, and small amounts combine with glucuronide for removal in the feces. The metabolic pathways for natural and synthetic opioids are shown in Figure 2.

The pharmacologic effects of opioids are attributed to their binding to specific receptors in the central nervous system. At least 3 major opioid receptor subtypes exist: mu, kappa, and delta.[4] Interactions of opioids with these receptors are associated with the clinical manifestations in Table 2. Opioids modulate cerebral cortical pain perception at supraspinal (brain), spinal, and peripheral levels. The mu receptors mediate most analgesic effects of morphine and related compounds within the brain (supraspinal analgesia).[5] Although interaction with kappa receptors produces analgesia in the spinal cord, psychomimetic effects (dysphoria) via kappa receptor interaction in the brain may also occur, thus limiting the clinical use of opioids.

The sigma receptor was once considered an opioid subtype.[6] Because the opioid antagonist, naloxone, has no effect, the sigma receptor is no longer grouped with opioid receptors.[7] The receptor does, however, have a role in opioid pharmacology because several key opioids, such as dextromethorphan and pentazocine, are sigma-receptor agonists.

Downloaded from https://academic.oup.com/labmed/article/31/6/334/2657111 by guest on 21 August 2022

Opioids are classified according to their mode of action as full agonists, mixed agonists-antagonists, and full antagonists. Full agonists have an affinity for a specific type of opioid receptor. Mixed agonist-antagonists have an agonistic effect with one class of receptor and an antagonistic effect with another. Full antagonists, via increased affinity or competitive binding, can prevent opioid binding or displace an opioid from its receptor. Full antagonists have a reduced analgesic effect. Naloxone is a potent antagonist with no analgesic effects.

Clinical Effects of Opioids

Opioids find use in many situations, including surgical and medical emergencies. They are used for anesthesia, sedation, and postoperative analgesia and to treat trauma and burns, pain in orthopedic and terminal illness, cough, and diarrhea. The major effects of opioids are on the central nervous system. Opioids provide analgesia without sedation, euphoria, or loss of consciousness. They also affect the pulmonary, cardiovascular, and gastrointestinal systems by causing respiratory depression, bradycardia, nausea, vomiting, and other classic symptoms associated with intoxication or withdrawal (Table 3).

Diagnosis of Opioid Intoxication

Although most clinical findings are nonspecific, a constellation of classic signs—mental depression, hypoventilation, miosis, and sometimes reduced bowel motility—called the "opioid toxidrome" often develops in patients with opioid intoxication. Differentiating acute opioid intoxication from other conditions with similar clinical presentation can be challenging. Besides the opioid syndrome, the readily treatable hypoglycemia, hypoxia, and hypothermia are often seen with opioid poisoning; these symptoms, however, can also occur with phencyclidine, phenothiazine, sedative-hypnotic (benzodiazepines), and clonidine poisoning. Although clinicians can often rule out some drugs on the basis of other signs and symptoms—nystagmus (phencyclidine), electrocardiographic changes (phenothiazine), normal vital signs and coma (benzodiazepines)—others such as clonidine are not so easily eliminated. Thus, a simple opioid-positive drug screen test result from the laboratory is most helpful.

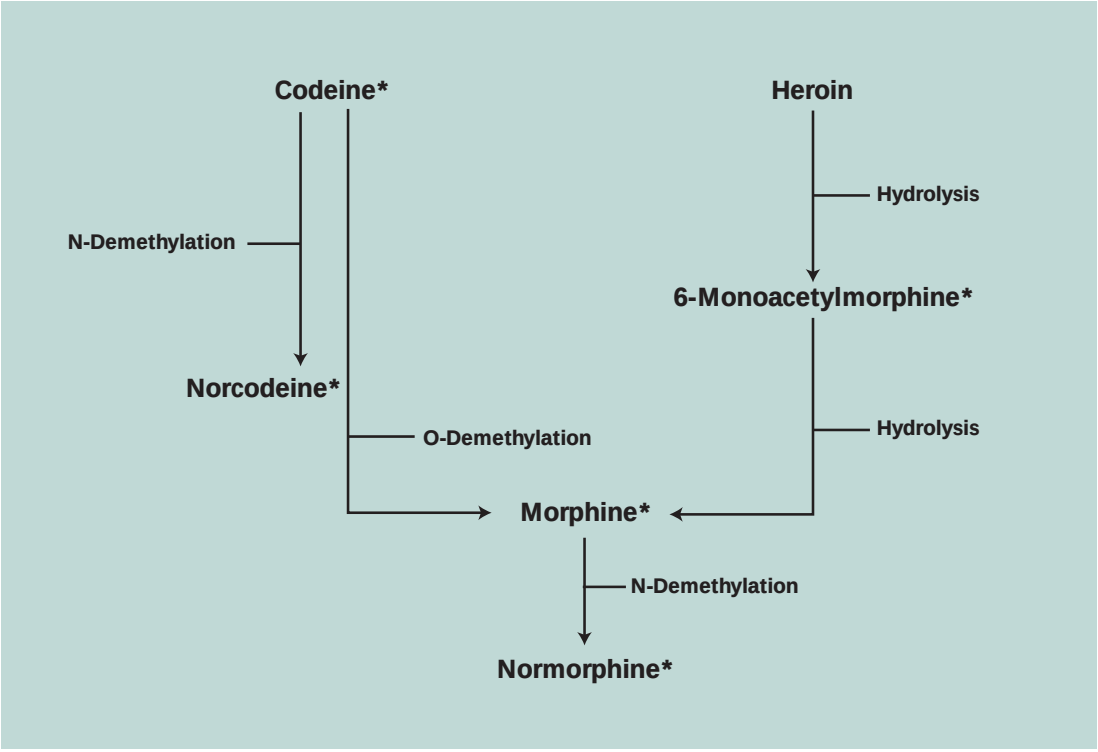


Fig 2. Schematic representation of metabolic profile of morphine, codeine, and heroin. *Indicates compounds conjugated with glucuronic acid and sulfate. From El Sohly MA, Jones AB. Origin of morphine and codeine in biological fluids. In: Liu RH, Goldberger BA, eds. *Handbook of Workplace Drug Testing*. Washington, DC: AACC Press; 1995:230. Used with permission.

Downloaded from https://academic.oup.com/labmed/article/31/6/334/2657111 by guest on 21 August 2022

Table 3. Clinical Findings in Opioid Intoxication and Withdrawal

Intoxication
Bradycardia
Coma
Decreased gastrointestinal tract motility
Depressed mental status
Depressed respiratory drive
Hypotension
Hypothermia
Miosis (ie, pupil contraction)
Needle track marks on skin
Withdrawal
Agitation
Diarrhea
Diaphoresis (ie, heavy perspiration)
Hypertension
Muscle cramps
Mydriasis (ie, pupil dilation)
Piloerection (ie, hair erection)
Tachycardia
Tachypnea (ie, rapid shallow breathing)
Vomiting
Yawning

Patient Management

The common methods to treat opioid intoxication are shown in Table 4. Other than treating the hypoglycemia, the first step is to reverse the central depression caused by the opioid. Naloxone, an opioid antagonist with a 20- to 30-minute half-life is usually used for this purpose. In most non–opioid-dependent patients with acute opioid overdose, small doses (0.1 to 0.4 mg) generally reverse the effects of intoxication. Although naloxone is safe even at high doses (10 mg), giving 0.4-mg doses to opioid-dependent patients often results in acute withdrawal, leading to significant stress for both patient and healthcare personnel (see Table 4). The initial doses for these patients should be small (0.1 mg), then increased to 0.4, 2.0, and 10 mg.[8] Emesis often accompanies acute withdrawal as well. If the patient does not immediately regain consciousness, additional complications such as head trauma or intoxication with ethanol or sedative-hypnotic agents may be present. If naloxone produces no response at all, the patient may require intubation and a computed tomography scan of the head to rule out cerebral bleeding or head trauma.

Opioids Requiring Special Consideration

Heroin

As the most widely abused opioid, heroin is synthesized by acetylating morphine, which increases the analgesic potency 2- to 3-fold. Heroin is often mixed (cut) with common diluents such as sugar, baking soda, flour, and talc. In the United States, "street purity" ranges from 10% to 80%, depending on geographic location. Peak plasma concentrations occur within a few minutes of drug administration. With a half-life of a few minutes, heroin is rarely detected in body fluids. The drug undergoes rapid deacetylation to 6-acetylmorphine (6-AM), a metabolite with 4 times the potency of morphine. Because heroin has no affinity for opioid receptors in the brain, its analgesic properties are due to the combined effects of 6-AM and its morphine metabolite. Death due to heroin administration is generally the result of profound respiratory depression.

The illicit transport of heroin between countries is a socioeconomic problem. Couriers of heroin (or cocaine), called "mules" or "body packers," ingest numerous multiply wrapped packages of concentrated drug, to have them later removed cathartically (Fig 3). Often asymptomatic, the drug transporters risk delayed or prolonged toxic effects if the packets rupture before they are removed. With the aid of abdominal radiography, emergency department physicians can confirm gastrointestinal smuggling,[9] though the radiographs do not reveal the packet contents. If the courier presents with symptoms suggestive of packet rupture, physicians treat according to history and lab results. Heroin cases require continuous naloxone infusion, whereas cocaine cases need surgery.[10]

Downloaded from https://academic.oup.com/labmed/article/31/6/334/2657111 by guest on 21 August 2022

Table 4. Treatment of Opioid Intoxication

▪ If hypoglycemic, administer oxygen, 50% dextrose.
▪ If comatose with suspected drug overdose, give direct opioid antagonist (naloxone): Initial dose 2-mg by intravenous "push" (restrain patient before administration because naloxone precipitates withdrawal); up to 10-mg dose with longer-acting opioids and higher grades of heroin; drip if repeated boluses required.
▪ If naloxone ineffective and patient remains comatose, consider other causes and be prepared to intubate and ventilate patient.
▪ If patient in withdrawal, give supportive care, intravenous fluids for hydration; consider giving clonidine or methadone or refer patient to substance abuse detoxification center.

Fentanyl

Fentanyl (Sublimaze), a short-acting, opioid agonist with 50 to 100 times the potency of morphine, is used widely in clinical medicine. Fentanyl and its illicit analogues (3-methyl fentanyl) are prevalent drugs of abuse in some regions of the United States.[11] Although they supposedly receive a more intense "rush" with heroin, long-term heroin users generally cannot distinguish fentanyl from heroin.[12] Epidemics of heroin-related deaths have been associated with heroin tainted with fentanyl analogue. One of the first occurred in Orange County, CA. The epidemic involved the fentanyl analogue, alpha-methylfentanyl, or "China White." Since then, similar epidemics have occurred in Pittsburgh (1998), Philadelphia (1992), and, most recently, in New York.[13] Typically, patients are comatose and apneic, and blood or urine analyses reveal no opioids.[14] Owing to their high potency (up to 6,000 times greater than morphine), high doses of naloxone may be needed to counteract the effects of alpha-methylfentanyl.

Codeine

A semisynthetic agent produced by the methylation of morphine, codeine has low-to-moderate analgesic properties. Even at low doses, the drug effectively suppresses cough.[15] Codeine is often formulated with nonopioid analgesics such as aspirin or acetaminophen. Between 10% and 20% is excreted unchanged, and 10% is metabolized to morphine (which accounts for most of its analgesic effects). Codeine conjugates are excreted before morphine conjugates. After 3 days of use, codeine metabolites resemble those associated with morphine or heroin use. The appearance of norcodeine in urine, however, indicates codeine use because heroin and morphine are not metabolized to norcodeine.

Propoxyphene

Like its structural analogue, propoxyphene binds to mu receptors to produce the clinical findings seen with opioid use. Propoxyphene and its active metabolite, norpropoxyphene, produce life-threatening respiratory arrest in an overdose situation. These compounds may also (1) produce cardiac toxic effects by blocking the fast sodium channels of the myocardium, and (2) precipitate seizures resulting from central nervous system toxic effects. When patients take an overdose of propoxyphene formulated with either acetaminophen (Darvocet-N) or salicylate, they become poisoned with the nonopioid analgesia-enhancing medications as well. In these cases, quantitative measurements of acetaminophen or salicylates are indicated.

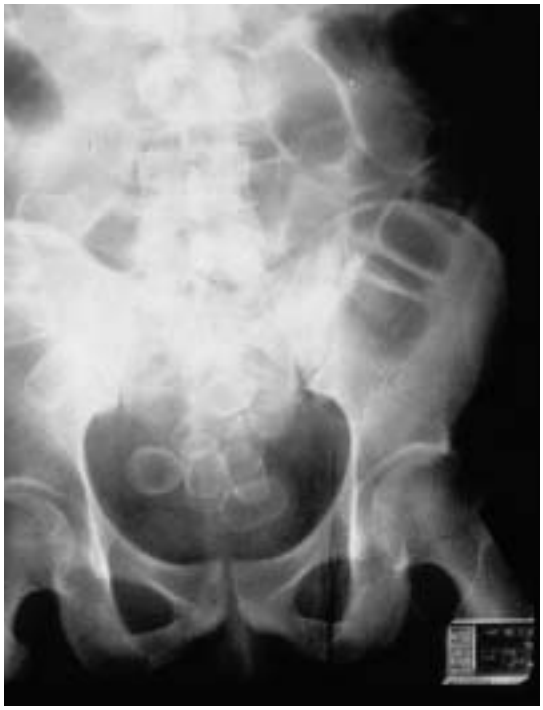
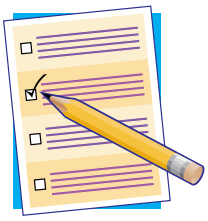


Fig 3. Abdominal radiograph shows numerous drug packets swallowed by a courier, or "body packer." The contents of the packets were later determined to be heroin.

Downloaded from https://academic.oup.com/labmed/article/31/6/334/2657111 by guest on 21 August 2022

Dextromethorphan

Like codeine, the opioid dextromethorphan is a cough suppressant. It is unlikely, however, that dextromethorphan exerts this effect through an opioid receptor. Unlike its potent optical isomer (levorphanol), dextromethorphan has no analgesic properties, although at high doses, it binds opioid receptors to produce miosis and depress the central nervous system. Dextrorphan, the metabolite of dextromethorphan, reacts with the sigma receptor to produce a psychosis similar to that obtained with phencyclidine.[16] In addition, urine from long-term dextromethorphan users or overdose patients produces false-positive immunoassay results for the structurally similar phencyclidine.



Test Your Knowledge!

Look for the CE Update exam on Drugs of Abuse (005) in the September issue of *Laboratory Medicine*. Participants will earn 3 CMLE credit hours.

Pentazocine

In the past, patients abusing pentazocine (Talwin) administered it with a blue capsule of tripelennamine. Consequently, abusers referred to the combination as "Ts and blues."[17] Pentazocine, despite its agonist-antagonist effects, remains widely abused when combined with methylphenidate.

Meperidine

Meperidine is not a prevalent illicit drug, although it is often used to treat acute or chronic pain. Long-term users, especially those with renal insufficiency, are at risk for toxic effects caused by the active hepatic metabolite normeperidine.[18] This metabolite is eliminated by the kidney and induces tremor, myoclonus, or seizures. Interacting primarily with opioid receptors, meperidine can also exert effects with other receptor classes. Most notable are its serotonin effects, particularly in patients receiving monoamine oxidase inhibitors. The excessive meperidine-induced release of presynaptic serotonin may produce the "serotonin syndrome" characterized by muscle rigidity, hyperthermia, altered mental status, and death.[19]

Diphenoxylate and Loperamide

Although structurally related to meperidine, diphenoxylate is insoluble, which limits its absorption from the gastrointestinal tract. This property, however, enhances its antidiarrheal effects resulting from its interaction with the gastrointestinal mu receptor. Diphenoxylate is combined with a small dose of atropine to augment these antidiarrheal properties.

When ingested by children, adult formulations containing diphenoxylate induce toxic effects. The onset is often delayed, most likely due to the production of the more potent liver metabolite, difenoxin, which has a longer serum half-life than diphenoxylate.[20]

Loperamide (Imodium) is another insoluble meperidine analogue used to treat diarrhea. The few cases of adverse outcomes suggest that this drug is safer to use than diphenoxylate.

Methadone

A mu agonist taken orally, methadone is a well-known maintenance drug for heroin addicts. As a legal drug, the long-acting opioid replaces the illicit heroin. Patients are given high therapeutic doses to prevent their surreptitious use of illicit drugs,[21] resulting in methadone overdose. When this occurs, symptoms similar to those of morphine overdose appear, but for longer periods (up to 24 hours). Unlike patients with uncomplicated heroin overdose (who are treated and discharged if asymptomatic for awhile[22]), methadone-overdose patients must be hospitalized to treat the prolonged toxic effects and to guard against their recurrence. In countries such as England, accidental ingestion of methadone by children is increasing and often ends in death.[23]

Laboratory Diagnosis of Opioid Poisoning

Besides ordering radiographic images for cerebral bleeding or electrocardiograms to monitor bradycardia, clinicians treating patients suspected of opioid overdose order arterial blood gases, electrolytes, glucose, renal function tests, and toxicology tests to confirm the presence of opioids or

Downloaded from https://academic.oup.com/labmed/article/31/6/334/2657111 by guest on 21 August 2022

compounds that may give rise to similar symptoms. Most opiate immunoassays are not specific owing to cross-reactivity with structurally related compounds. Overall specificity of immunoassays depends on the antibody characteristics and whether the assay is homogeneous or heterogeneous. Although qualitative urine drug screen tests are helpful, opioid-negative results do not rule out the presence of opioids. The interpretation of qualitative urine drug screening tests is often based on cutoff values, below which the result is considered negative for the drug in question. Because an opioid may not react significantly with the assay antibody, or, like the potent opioid fentanyl, it may exist at undetectable low levels in the blood, clinicians should not assume that this negative result rules out the presence of the drug. This is not necessarily an issue in workplace testing; although in the emergency setting, the presence of any drug may help to explain a patient's toxic symptoms. Fortunately, drug intoxication levels in emergency situations are much higher than the cutoff values used by most laboratories.

In the workplace, the selection and application of cutoff values is different because many factors other than drug abuse have caused false-positive results. For example, ingestion of moderate-to-large amounts of poppy seeds on bagels produced false-positive result for opioids, especially when the test was done 2 hours after ingestion.[24,25] These seeds, which contain codeine and morphine, are often used for culinary purposes and come from poppy plants similar to *P somniferum*. Another cause of false-positive opioid results was the use of prescribed medications containing morphine or codeine. For these reasons the US Department of Health and Human Services, in federally regulated drug testing programs, raised the opioid cutoff value from 300 to 2,000 ng/mL for immunoassay tests. For gas chromatography–mass spectrometry confirmation of codeine and morphine, the department raised the cutoff value to the same levels.[26]

The federal government made these changes for 2 reasons: (1) to detect morphine and codeine and (2) to confirm illicit heroin use. Thus testing for the heroin metabolite 6-AM became mandatory with the confirmation cutoff level set at 10 ng/mL.[26] The presence of the 6-AM is important because human beings cannot acetylate morphine to make monoacetylmorphine, but they can deacetylate heroin (diacetylmorphine) to form 6-AM. For this reason, the presence of 6-AM is unequivocal evidence of heroin use. One drawback with 6-AM is its short urinary half-life, which limits detection time to approximately 2 to 8 hours.

Conclusion

Patients brought to the emergency department with opioid intoxication receive rapid clinical diagnosis and treatment owing to the uniqueness of the opioid toxidrome. Although urine drug screen tests do not identify specific opioids, they confirm their presence, which aids the clinician in prescribing treatment. However, a urine drug screen test negative for opioids does not rule out the presence of opioids such as fentanyl, which is effective at low concentrations in biologic fluids and often nondetectable by most routine screening techniques.

References

1. Mann J. *Murder, Magic and Medicine*. Oxford, England: Oxford University Press; 1995.
2. Kerrigan S, Goldberger BA. Opioids. In: Levine B, ed. *Principles of Forensic Toxicology*. Washington, DC: American Association for Clinical Chemistry Press; 1999:202-220.
3. Jenkins AJ, Keenan RM, Henningfield JE, et al. Pharmacokinetics and pharmacodynamics of smoked heroin. *J Anal Toxicol*. 1994;18:317-330.
4. Minami M, Satoh M. Molecular biology of the opioid receptors: structures, functions and distributions. *Neurosci Res*. 1995;23:121-145.
5. Pasternak GW. Multiple morphine and enkephalin receptors and the relief of pain, *JAMA*. 1988;259:1362-1367.
6. Martin WR, Eades CG, Thompson JA, et al. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther*. 1976;197:517-532.
7. Walker JM, Bowen WD, Walker OF, et al. Sigma receptors: biology and function. *Pharmacol Rev*. 1990;42:355-399.
8. Nelson LS. Opioids. In: Goldfrank LR, Flomenbaum NE, Lewin NA, et al, eds. *Goldfrank's Toxicologic Emergencies*. 6th ed. Stamford, CT: Appleton & Lange; 1998:976-995.

Downloaded from https://academic.oup.com/labmed/article/31/6/334/2657111 by guest on 21 August 2022

9. Hierholzer J, Cordes M, Tantow H, et al. Drug smuggling by ingested cocaine filled packages: conventional x-ray and ultrasound. *Abdom Imaging*. 1995;20:333-338.

10. Goldfrank L, Weisman RS, Errick JK, et al. A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med*. 1986;15:566-570.

11. Ziporyn T. A growing industry and menace: makeshift laboratory's designer drugs. *JAMA*. 1986;256:3061-3063.

12. LaBarbera M, Wolfe T. Characteristics, attitudes and implication of fentanyl use based on reports from self-identified users. *J Psychoactive Drugs*. 1983;15:293-301.

13. National Institute on Drug Abuse. *Designer Drugs*. Rockville, MD: National Institute on Drug Abuse; September 1993. NIDA capsule C-86-5.

14. Brittain JL. China White: the bogus drug. *J Toxicol Clin Toxicol*. 1982;19:1123-1126.

15. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, Molinoff PB, et al, eds. *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*. 9th ed. New York, NY: McGraw-Hill; 1996:521-556.

16. Szekely JI, Sharpe LG, Jaffe JH. Induction of phencyclidine-like behavior in rats by dextrophan but not dextromethorphan. *Pharmacol Biochem Behav*. 1991;40:381-384.

17. DeBard ML, Jagger JA. "T's and B's": midwestern heroin substitute. *Clin Toxicol*. 1981;18:1117-1123.

18. Kaiko RF, Foley KM, Grabinski PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol*. 1983;13:180-185.

19. Browne B, Linter S. Monoamine oxidase inhibitors and narcotic analgesics: a critical review of the implications for treatment. *Br J Psychiatry*. 1987;151:210-212.

20. Karim A, Ranney RE, Evensen KL, et al. Pharmacokinetics and metabolism of diphenoxylate in man. *Clin Pharmacol Ther*. 1972;13:407-419.

21. Strain EC, Stitzer ML, Liebson IA, et al. Dose-response effects of methadone in the treatment of opioid dependence. *Ann Intern Med*. 1993;119:23-27.

22. Smith Da, Leake L, Loflin JR, et al. Is admission after intravenous heroin overdose necessary? *Ann Emerg Med*. 1992;21:1326-1330.

23. Binchy JM, Molyneus EM, Manning J. Accidental ingestion of methadone by children in Merseyside. *BMJ*. 1994;308:1335-1336.

24. el Sohly H, el Sohly M, Stanford D. Poppy seed ingestion and opiates urinalysis: a closer look. *J Anal Toxicol*. 1990;14:308-310.

25. Selavka CM. Poppy seed ingestion as a contributing factor to opiate-positive urinalysis results: the Pacific perspective. *J Forensic Sci*. 1991;36:685-696.

26. *Federal Register*, September 30, 1997.

Downloaded from https://academic.oup.com/labmed/article/31/6/334/2657111 by guest on 21 August 2022