Opioids

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There has been no greater disruption of modern civilizations as the insidious havoc brought upon them by the addictive potential of opioid compounds and their derivatives.

From the introduction of opium into China in the 17th century, resulting in the undermining of its organized system, to the modern-day pharmaceutical production of synthetic narcotic analgesics, these compounds have infiltrated urban and rural societies.

Today, narcotic addiction permeates all socioeconomic classes, from economically underserved communities to affluent neighborhoods to the U.S. armed forces.

Among the substances most frequently involved in toxic human exposures, analgesics, with or without narcotic components, account for 14% and 11.7% of all adult and human exposures, respectively.

The increase is largely due to the illicit use of prescription pain relievers such as oxycodone and hydrocodone.

These compounds are not necessarily obtained only through illicit drug dealing (street drugs), but their supply is abundant due to fraudulent and illegitimate prescriptions, as well as in the course of overprescribing practices.

Health care professionals are also particularly vulnerable to the addictive potential of narcotics, principally due to easy accessibility.

Initial narcotic ingestion is often an unpleasant experience.

Patients usually complain of nausea, dizziness and muscular weakness.

With continued use, individuals build tolerance to the unpleasant adverse reactions in preference to the euphoric effects.

Opioid compounds are ingested orally in tablet or capsule form, the most common method of administration (considering both therapeutic and illicit drug use).

As greater tolerance develops, ingesting the same amount of drug does not produce euphoria as initially experienced, necessitating either higher doses or an alternate, more immediate method of administration.

This includes rendering the tablets to a powder, or using a reformulated powder form, for nasal insufflation (snorting), for injection subcutaneously (skin popping) or intravenously.

Classification

By definition, opiates, as a class, exert their pharmacological effects at opioid receptors, whereas opioids are alkaloid extracts of the opium poppy.

Opium, the parent crude form of the naturally occurring compounds, is derived from the milky exudates of the unripe capsule of *Papaver somniferum L.* (opium poppy).

The plant is cultivated in the Mediterranean and Middle East regions, India and China.

About two dozen alkaloids, of which morphine occupies about 10%, are formed primarily in various cells of the plant.

Interestingly, the very small seeds of the plant do not contain opium.

Few pharmacological and toxicological differences exist between the classes.

Some pharmacokinetic properties, however, distinguish the compounds, especially among the many narcotic derivatives.

Mechanism of Toxicity

The mechanism of opiate toxicity is an extension of its pharmacology and is directly related to interaction with stereospecific and saturable binding sites or receptors in central nervous system tissues, including the cerebrum, limbic system, basal ganglia and brain stem.

These receptors are classified according to the empirical observations noted for the variety of opioid effects.

The opioid receptors are biologically active sites of several endogenous ligands, including the two pentapeptides, methionine-enkephalin and leucine-enkephalin.

Three receptor classes have been identified:

1. Compounds that selectively bind to the *μ-receptor* exhibit morphine-like analgesia, euphoria, respiratory depression, miosis, partial gastrointestinal inhibition and sedative effects.

2. Narcotic antagonists such as pentazocine, nalorphine and levorphanol appear to bind to the *k-receptor*, although analgesia, sedation, delusion, hallucinations, GI inhibition and miotic effects still persist.

3. Pentazocine and nalorphine are also described as having affinity for the *δ-receptors* although this binding is primarily associated with dysphoria and mood changes.

Toxicokinetics

Morphine is rapidly absorbed from an oral dose, and from intramuscular and subcutaneous injections.

Peak plasma levels occur at 14 to 60 minutes and 14 minutes, respectively.

Morphine is metabolized extensively, with only 2% to 14% excreted as the parent molecule, while 60% to 80% is excreted in the urine as the conjugated glucuronide.

Heroin is rapidly biotransformed first to monoacetylmorphine and then to morphine.

Both heroin and monoacetylmorphine disappear rapidly from the blood (t½=3 minutes, 5–10 minutes, respectively).

Thus, morphine levels rise slowly, persist longer, and decline slowly.

Codeine is extensively metabolized, primarily to the glucuronide conjugate.

About 10% to 14% of a dose is demethylated to form morphine and norcodeine conjugates.

Therefore, codeine, norcodeine and morphine in free and conjugated forms appear in the urine after codeine ingestion.

Mechanism of Toxicity

Clinical signs and symptoms correlate with the highest concentrations of binding sites in CNS and other tissues.

The limbic system, thalamus, corpus striatum, hypothalamus, midbrain, and spinal cord have the highest concentrations.

Analgesia appears to affect spinal ascending and descending tracts, extending up to the midbrain.

Mood, movement, and behavior correlates with interaction with receptors in the basal ganglia, while mental confusion, euphoria, or dysphoria alter neuronal activity in the limbic system.

Hypothalamic effects are responsible for hypothermia.

Miosis is thought to occur from μ-receptor stimulation.

Signs and Symptoms of Clinical Toxicity

The clinical presentation of the opioid is characterized by CNS depression (including coma), miosis and respiratory depression.

Miosis is generally an encouraging sign since it suggests that the patient is still responsive.

Respiratory depression is a result of depressed brain stem and medullary respiratory centers, responsible for maintenance of normal rhythm.

μ-receptor agonists depress respiration in a dose-dependent manner, and can lead to respiratory arrest within minutes.

Fifty percent of acute opioid overdose is accompanied by a noncardiogenic pulmonary edema responsible for the majority of fatalities.

The condition involves loss of consciousness and hypoventilation, probably resulting from hypoxic, stress-induced, pulmonary capillary fluid leakage.

Peripheral effects include bradycardia, hypotension and decreased GI motility.

Urine output also diminishes as a consequence of increased antidiuretic hormone (ADH) secretion.

Clinical Management of Acute Overdose

Maintenance of vital functions, including respiratory and cardiovascular integrity, is of paramount importance in the clinical management of acute opioid toxicity.

Gastric lavage and induction of emesis are effective if treatment is instituted soon after ingestion.

It is possible to reverse the respiratory depression with opioid antagonists.

Naloxone is a pure opioid antagonist.

Naloxone is also indicated in the diagnosis of suspected acute opioid overdose.

Depending on the extent of narcotic overdose, a continuous infusion of naloxone may be required, especially in the presence of opioids with longer half-lives, such as propoxyphene or methadone.

As respiration improves, naloxone, which has a half-life of 60 to 90 minutes, may be discontinued and resumed, as necessary.

If there is no response after 10 mg of naloxone, concomitant ingestion with other depressants is likely.

It should be noted that naloxone is of little benefit in reversing noncardiogenic pulmonary edema.

Naltrexone is also a pure opioid antagonist available as oral tablet dosage form only.

A 50-mg dose of naltrexone blocks the pharmacological effects of opioids by competitive binding at opioid receptors.

It is also indicated in the treatment of alcohol dependence.

Naltrexone has been noted to induce hepatocellular injury when given in excess.

Nalmefene, available in 1mg/mL and 100µg/mL ampoules, is indicated for the complete or partial reversal of natural or synthetic opioid effects.

It is a 6-methylene analog of naltrexone.

Nalmefene has been associated with cardiac instability, although this reaction appears to be the result of abrupt reversal of opioid toxicity.

Several drugs have agonist activity at some receptors (k) and antagonist activity at other (μ) receptors.

Nalbuphine is a potent analgesic with narcotic agonist and antagonist actions.

Other mixed agonist-antagonist compounds are designated as partial agonists, such as butorphanol, buprenorphine and pentazocine.

These compounds are potent analgesics and weakly antagonize the effects of opioids at the μ-receptor, while maintaining some agonist properties at the k- and δ-receptors.

Tolerance and Withdrawal

The Department of Mental Health and Substance Dependence at the World Health Organization (WHO), in collaboration with the U.S. National Institute on Drug Abuse (NIDA), defines several terms important in understanding drug abuse and the phenomena of tolerance and withdrawal.

Addiction involves compulsive psychoactive drug use with an overwhelming involvement in the securing and using of such drugs.

The withdrawal syndrome occurs as a result of sudden or abrupt discontinuation of the substance.

Compulsive drug use involves the psychological need to procure and use drugs, often referred to as craving.

In this case, the uncontrollable drive to obtain the drugs is necessary to maintain an optimum state of well-being.

Habituation refers to psychological dependence.

Physiological dependence involves the need for repeated administration to prevent the withdrawal syndrome.

In fact, with repeated chronic dosing, seizure threshold for opiate narcotics is elevated, threatening the precipitation of seizure upon withdrawal (rebound effect).

With repeated administration, addicted individuals necessitate greater amounts of drug to achieve the desired effect.

Conversely, the euphoric effect is markedly diminished with continued use of the same amount of drug.

Since various pharmacological effects on different organ systems are not uniformly distributed, tolerance is not evenly demonstrated.

While a diminished effect continues with progressive tolerance, the increasing doses threaten induction of respiratory depression.

Increased metabolism and adjustment to the sedative, analgesic, and euphoric effects are proposed as possible mechanisms for the development of tolerance that is, the physiological drive to achieve homeostasis.

Depending on the drug and the intensity and severity of the addiction, the withdrawal syndrome is precipitated hours after the last narcotic dose, with peak intensity occurring at about 72 hours.

The intensity of the syndrome is greatest with heroin, followed by morphine and methadone.

Heroin withdrawal is characterized by acute, sudden symptoms of greater vigor, while methadone withdrawal is distributed over 7 to 10 days and is of lower intensity.

The development of muscle spasms has come to define the syndrome, commonly known as “kicking the habit”.

Although the syndrome is rarely fatal, administration of an opioid at any time and at relatively low doses during withdrawal alleviates the condition.

Casual, habitual, uncontrolled use of prescription narcotics often follows the “medical addict.”

The cyclic behavior is characterized by excessive use of the drugs followed by a period of abstinence and is often accompanied by subtle signs and symptoms of withdrawal.

The withdrawal experience in this case is often indistinguishable and unrecognizable by both patients and health care professionals and may be mistaken with other low grade indicators.

For example, within 24 hours after the last opioid dose, patients may experience anxiety, irritability, abdominal cramps, diaphoresis, insomnia and joint pain.

Nevertheless, these are warning signs of the development of tolerance and withdrawal and should be deemed, understood, and accepted as a chronic disease.

Characterization of the Opioid Withdrawal Syndrome

Stage	Time after last dose	Signs and symptoms
Anticipatory	3–4 hr	Withdrawal fear, craving, compulsive drug-seeking behavior
Early withdrawal	8–12 hr	Lacrimation, sweating, listless behavior, anxiety, restlessness, stomach cramps
	12–16 hr	Restless sleep, nausea, vomiting, mydriasis, anorexia, tremors; cold clammy skin, fever, chills; compulsive drug-seeking behavior
	48–72 hr	Peak intensity; tachycardia, hypertension, hypothermia, piloerection (goose bumps, *cold turkey*), muscle spasms; continued nausea, vomiting, dehydration, compulsive drug-seeking behavior; risk of cardiovascular collapse
Protracted abstinence	6 mo	Stimulus-driven cravings, anorexia, fatigue, bradycardia, hypotension

Clinical Management of Addiction

The risks and benefits of traditional medical detoxification associated with the use of methadone and narcotic antagonists are presented.

Although methadone treatment programs have shown some success in opioid detoxification, significant progress in therapeutic intervention has resulted more recently using buprenorphine.

Buprenorphine is the first opioid drug approved under the Drug Addiction Treatment Act (DATA) for the treatment of opioid dependence in an office-based setting.

The drug, a partial opioid agonist, is dispensed for outpatient use and administered sublingually, sometimes in combination with naloxone, the full opioid antagonist.

The antagonist blocks μ-receptors, thus precipitating the withdrawal syndrome.

Buprenorphine reduces illicit opioid use and helps patients remain in treatment programs by increasing availability of treatment options, suppressing symptoms of opioid withdrawal, and decreasing cravings for opioids.