
بسم الله الرحمن الرحیم

دکتر میر سعید رمضانی

متخصص طب اورژانس

هیات علمی دانشگاه علوم پزشکی بابل

opioids

Opioids

- are available in various formulations that allow administration by virtually any route:

- epidural, inhalational, intranasal, intrathecal, oral, parenteral (i.e., subcutaneous {SC}, intravenous {IV},intramuscular {IM}), rectal, transdermal, and transmucosal.

Classification

Natural (opiates)	Heroin Codeine Morphine
Semi-synthetic	Buprenorphine Hydrocodone Hydromorphone Oxycodone Oxymorphone
Synthetic	Diphenoxylate Fentanyl Meperidine Methadone Pentazocine Propoxyphene Tramadol

TABLE 38–1. Clinical Effects Related to Opioid Receptors

1996 Conventional Name	Proposed IUPHAR Name	IUPHAR Name	Important Clinical Effects of Receptor Agonists
μ_1	OP_{3a}	MOP	Supraspinal analgesia Peripheral analgesia Sedation Euphoria Prolactin release
μ_2	OP_{3b}		Spinal analgesia Respiratory depression Physical dependence GI dysmotility Pruritus Bradycardia Growth hormone release
κ_1	OP_{2a}	KOP	Spinal analgesia Miosis Diuresis
κ_2	OP_{2b}		Psychotomimesis Dysphoria
κ_3	OP_{2b}		Supraspinal analgesia
δ	OP_1	DOP	Spinal and supraspinal analgesia Modulation of μ-receptor function Inhibit release of dopamine
Nociceptin/ orphanin FQ	OP_4	NOP	Anxiolysis Analgesia

GI, gastrointestinal; IUPHAR, International Union of Pharmacology Committee on Receptor Nomenclature.

TABLE 33-3 Selective Activity of the Main Opiate/Opioid on the Different Opioid Receptors

MOLECULES	ACTIVITY	μ RECEPTOR	δ RECEPTOR	κ RECEPTOR
Morphine	Agonist	+++		+
Methadone	Agonist	+++		
Etorphin	Agonist	+++	+++	+++
Fentanyl	Agonist	+++		
Sufentanyl	Agonist	+++	+	+
Buprenorphine	Agonist–antagonist	P	?	– –
Nalorphin	Agonist–antagonist	– – –		+
Pentazocin	Agonist–antagonist	P		++
Naloxone	Antagonist	– – –	–	– –
Naltrexone	Antagonist	– – –	–	– – –
Endogenous Peptides*				
Met- et Leu-enkephalins	Agonist	++	+++	
β-endorphin	Agonist	+++	+++	
Dynorphin A	Agonist	++		+++
Dynorphin B	Agonist	+	+	+++
α-neoendorphin	Agonist	+	+	+++

*Enkephalins and endorphins are considered the endogenous ligands of μ and δ receptors; dynorphin A activity is related to κ receptors.
+, agonist; –, antagonist; P, partial agonist; ?, not determined.

TABLE 38–2. Clinical Effects of Opioids

Cardiovascular	Bradycardia
	Orthostatic hypotension
	Peripheral vasodilation
Dermatologic	Flushing (histamine)
	Pruritus
Endocrinologic	Reduced antidiuretic hormone (ADH) release
	Prolactin release
	Reduced gonadotrophin release
Gastrointestinal	Increased anal sphincter tone
	Increased biliary tract pressure
	Reduced gastric acid secretion
	Reduced motility
Neurologic	Analgesia
	Antitussive
	Euphoria
	Sedation, coma
	Seizures (meperidine, propoxyphene)
Ophthalmic	Miosis
Pulmonary	Acute lung injury
	Bronchospasm (histamine)
	Respiratory depression

TOXIC EFFECTS

opioid syndrome

Mental status depression,

Hypoventilation,

Miosis,

are the classic elements.

Opiate equivalents

Opiod	Parenteral	Oral
Morphine	5mg IM/IV/SC	15mg
Codeine	n/a	150mg
Fentanyl	75-100mcg	n/a
Oxycodine	5mg IV/SC	10mg
Tramadol	50mg IM/IV	75mg

Opioid screens

- A qualitative urine opioid screen may aid in the diagnosis, but available tests have limitations.
- the semisynthetic opioids **hydrocodone** and **oxycodone** are usually not detected by urine opioid screens, and essentially all synthetic opioids also are not routinely detected.
- **Rifampin**, **rifampicin**, **quinine**, **diphenhydramine**, and **fluoroquinolones** have been reported to cause false-positive urine opioid screen results.
- An opioid analogue, **dextromethorphan**, can produce a positive result on the urine opioid screen.

Opioid screens

- false-positive result with the methadone urine drug screen:

  Chlorpromazine
  Clomipramine
  Diphenhydramine
  Doxylamine
  Ibuprofen
  Quetiapine
  Thioridazine
  verapamil

- A urine opioid screen can be positive up to **2 to 3 days** after a single use of codeine, morphine, or heroin and methadone.

Treatment

- Airway protection and ventilatory maintenance are the most important treatment steps for opioid intoxications, because respiratory depression is the major morbidity and the cause of essentially all the mortality.
- Use bag-valve mask ventilatory support as needed to initially maintain adequate oxygenation and ventilation.
- After adequate ventilation is ensured, administer naloxone
- In fully awake patients or after the airway is protected with an endotracheal tube in unresponsive patients, administer single-dose activated charcoal, 1 gram/kg PO, if an opioid ingestion occurred within the hour.

Treatment

TABLE 186-2 Opioid Antagonists

Drug	Route	Initial Dose*	Onset of Action	Duration of Action†
Naloxone	IV	0.1–0.4 milligrams if breathing spontaneously	1–2 min	20–90 min
		2 milligrams if apneic		
	IM or SC	2 milligrams	5–6 min	
	Intranasal	2 milligrams (1 milligram in each nostril)	6–8 min	
	Nebulized	2 milligrams in 3 mL normal saline	5 min	
Nalmefene	IV	0.1–0.5 milligrams if breathing spontaneously	2–5 min	Up to 4 h
		2 milligrams if apneic	2–5 min	8 h
	IM or SC	1 milligram	5–15 min	4–6 h
Naltrexone	PO	50 milligrams	30–60 min	24 h
		100 milligrams	30–60 min	48 h
		150 milligrams	30–60 min	72 h

- To calculate the naloxone continuous infusion dose, determine the “wake-up dose” and administer **two thirds** of that dose per hour by IV infusion.

Disposition

- Naloxone-responsive injection drug users with presumed **heroin** intoxication can be safely discharged **1 to 2 hours** after administration of naloxone if they have:

  independent mobility

  oxygen saturation on room air >92%

  respiratory rate >10

  breaths/min

  pulse rate >50 beats/min

  normal temperature

  GCS=15

- In cases of exposure to opioids other than heroin, an observation period of **4 to 6 hours** in the ED is recommended after the last naloxone administration.
- In long-acting opioid overdose, observation should be extended for a minimum of **8 hours**.

Buprenorphine

- Buprenorphine (Subutex), a partial u-opioid agonist.
- Buprenorphine has high affinity for and slow dissociation from the μ-receptor, which results in a long duration of action.
- Furthermore, other opioid agonists (such as heroin) or antagonists (such as naloxone) cannot easily displace buprenorphine.
- Buprenorphine has poor oral bioavailability because of extensive first pass metabolism and is therefore administered SL or parenterally

Buprenorphine

- Buprenorphine can be associated with three distinct clinical scenarios:

  1- opioid-naïve patient

  2- opioid-dependent patient

  3- opioid dependent patient undergoing withdrawal

Methadone

- Methadone is synthetic opioid used as replacement therapy in opioid dependence and for chronic pain.
- The initial analgesic duration is 4 to 8 hours with an elimination half-life of 12 to 18 hours.
- With repetitive dosing, analgesic action duration and elimination half-life increase to about 22 to 36 hours and up to 59 hours, respectively.
- Interactions between methadone and HIV medications
- Ciprofloxacin, fluconazole, ketoconazole, and omeprazole can increase toxicity.
- Macrolide (especially clarithromycin), phenobarbital, phenytoin, spironolactone, and verapamil can precipitate withdrawal.
- Methadone and QT interval prolongation

Tramadol

- Tramadol overdoses are associated with lethargy, nausea, tachycardia, and seizures.
- At doses exceeding 500 milligrams, coma, hypertension, respiratory depression, and apnea are seen.
- Serotonin syndrome have been seen in isolated tramadol overdoses.
- Tramadol-induced seizures are common, and naloxone is ineffective in preventing them.

DIPHENOXYLATE HYDROCHLORIDE–ATROPINE SULFATE

- Anti-diarrheal agent
- Overdose
  - Initial phase: the anticholinergic toxidrome dominates
  - The second phase of intoxication is characterized by the opioid toxidrome.
- Children <6 years of age can be symptomatic after ingestion of a single tablet.
- In pediatric patients, absorption can be delayed up to 6 to 12 hours in some cases because of the effect of atropine on GI motility.
- Current recommendations are that all children <6 years of age be admitted to the hospital and be closely observed for 24 hours.
- Older children and adults should be observed in the ED for 6 hours.


با تشکر از توجه شما