

**МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ**  
**Харківський національний медичний університет**

## **OPIOID ANALGESICS**

*Methodical recommendations  
for students of English medium*

## **НАРКОТИЧНІ АНАЛЬГЕТИКИ**

*Методичні вказівки  
для студентів з англійською мовою навчання*

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## OPIOID ANALGESICS

**Analgesics** (pain killer) – are the drugs that reversibly and selectively inhibit pain without significant changing of consciousness.

**Analgesics are categorized as:**

1. *Nonopioid analgesics (nonopioids)*: acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and other salicylic acid derivatives.

2. *Opioid analgesics (opioids)*: mu opioid agonists (i.e., morphine-like agonists) and agonist- antagonist opioids.

3. *Adjuvant analgesics or co-analgesics*: a diverse group of drugs, with primary indications for conditions other than pain, with analgesic properties relevant to some conditions. Commonly used adjuvant analgesics include antiepileptic drugs, tricyclic antidepressants, anxiolytics and local anesthetics.

Management of pain is one of clinical medicine's greatest challenges.

**Pain** is defined as an unpleasant sensation that can be either acute or chronic and that is a consequence of complex neurochemical processes in the peripheral and central nervous system (CNS). Pain is a signal about the danger for the organism thus, it plays protective role. At the same time, it causes discomfort, decreases the quality of life, may be unbearable, and may cause a pain shock.

### MAIN QUESTIONS

1. Definition of analgesics
2. Significance of pain
3. Nociceptive system
4. Antinociceptive system
5. Opioid receptors and their endogenous ligands
6. Classification of opioid analgesics
7. Mechanism of opioid analgesics (narcotic) action
8. Pharmacokinetics of morphine
9. Peculiarities of other preparations
10. Therapeutic uses of opioid analgesics:
11. Adverse effects
12. Contraindications:
13. Acute morphine poisoning
14. Antagonists

### Nociceptive system

*Nociception* is pain perception. There is a special system for pain perception. **Nociceptive system** it includes sensitive nerve endings, sensory neuron in dorsal root, afferent nerves, and afferent pathways in the spinal cord, thalamus, and the somatosensory cortex. Thalamus is the main collector of pain impulses.

Ascending pain pathways traveling to thalamus and then to somatosensory cortex make numerous contacts by collaterals on many brain structures such as reticular formation, autonomic centers, limbic systems, motor cortex structures. Due to this pain sensation may be accompanied by tachycardia, increase in BP, rapid breathing, sweating, negative emotions, and behavioural reactions. The extent of these reactions depends upon the intensity of pain.

When nociceptive terminal of primary sensory neuron is stimulated by noxious stimuli action potential is generated, it passes along the peripheral afferent sensory fiber and arrives at junctions between the peripheral afferent fibers and the spinal cord neurons in the dorsal horn. The arrival of the action potentials causes the opening of voltage-gated  $\text{Ca}^{++}$  channels in the pre-synaptic membrane. An increased influx of  $\text{Ca}^{++}$  causes vesicles containing neurotransmitter to release their contents into the synaptic cleft. Neurotransmitter (pain mediators are primarily substance P, 1-glutamate, cholecystokinin, somatostatin, and bradykinin) binds to receptor on the postsynaptic membrane. Activation of such receptor enables the efflux of  $\text{K}^+$  and influx of  $\text{Ca}^{++}$  and  $\text{Na}^+$  into the postsynaptic cell membrane leading to the transmission of impulses along the axons of the spinal cord neurons to the brain. Information about pain is received and processed by higher centers in the brain and the individual perceives pain.

### **Antinociceptive system**

Antinociceptive system is a pain-suppressing network of neuron located in the mesencephalon and medulla. It inhibits the activity of spinal nociceptive neurons by descending pathways. This system includes neurons located in periaqueductal gray matter (PAG) of the mesencephalon, neurons in the rostral ventral medulla (RVM) and in nucleus raphe magnus (NRM). There is important functional interaction between nociceptive and antinociceptive systems due to availability of collaterals. Antinociceptive system is activated by impulses running from pain receptors to thalamus and cortex. Antinociceptive system operates through different types of receptors and neurotransmitters including one of the most important family of opioid receptors and their ligands.

### **Opioid receptors**

Opioid receptors (OR) – analgesic R are binding sites for endogenous opiates and opioid analgesics. They are located on the presynaptic membrane. There are several types of these receptors: mu ( $\mu$ -), kappa ( $\kappa$ -), sigma ( $\sigma$ -), delta ( $\delta$ -), epsilon ( $\epsilon$ -) receptors, which have different functional significance. All OR are members of the G protein-coupled receptor family and inhibit adenylyl cyclase. They are also associated with ion channels, increasing postsynaptic  $\text{K}^+$  efflux (hyperpolarization) or reducing presynaptic  $\text{Ca}^{2+}$  influx, thus neuronal firing and transmitter release.

### Distribution of receptors

- **Brainstem.** OR influence respiration, cough, nausea and vomiting, blood pressure, pupillary diameter, and control of stomach secretions.

- **Medial thalamus.** This area mediates deep pain that is poorly localized and emotionally influenced.

- **Spinal cord.** Receptors in the substantia gelatinosa are involved in the receipt and integration of incoming sensory information, leading to the attenuation of painful afferent stimuli.

- **Hypothalamus.** Receptors here affect neuroendocrine secretion.

- **Limbic system.** The greatest concentration of opiate receptors in the limbic system is located in the amygdala. These receptors probably do not exert analgesic action, but they may influence upon emotional behavior.

- **Periphery.** Opioids also bind to peripheral sensory nerve fibers and their terminals. As in the CNS, they inhibit  $Ca^{2+}$ -dependent release of excitatory, proinflammatory substances (for example, substance P) from these nerve endings.

- **Immune cells.** Opioid-binding sites have also been found on immune cells. The role of these receptors in nociception (response or sensitivity to painful stimuli) has not been determined.

- **Gastrointestinal tract (GIT).** Opioid-binding sites have also been found on myenteric plexus neurones in G.I.T. The roles of these receptors are to mediate reducing of G.I. motility.

- **Urinary bladder.** OR have also been found in the smooth muscles of detrusor and sphincter. Stimulation of these OR leads to contraction of ureter and increase in tone of urinary bladder smooth muscles.

### Endogenous opioid peptides

Three families of endogenous opioid peptides have been described in details: the **endorphins**, the pentapeptide **enkephalins** methionine-enkephalin (met-enkephalin) and leucine-enkephalin (leu-enkephalin), and the **dynorphins**. The three families of OR have overlapping affinities for these endogenous peptides.

### CLASSIFICATION OF OPIOID ANALGESICS

#### 1. Natural opium alkaloids

Morphine, Codeine

#### 2. Semi-synthetic opioids

Hydromorphone, Hydrocodone, Ethylmorphine, Pholcodeine

#### 3. Synthetic opioids

Methadone, Pethidine (Meperidine), Pentazocine, Trimeridine (Promedol), Fentanyl, Sulfentanyl, Dextropropoxyphene, Ethoheptazine, Buprenorphine, Propoxyphene

The disparities between opioids regarding efficacy and potential for dependence reflect differing affinity and intrinsic activity profiles for the individual receptor subtypes. There are strong agonists of opioid receptors, partial agonists, and agonist-antagonists of these receptors.

**Full agonists** (*have affinity for binding plus efficacy*)

- 1.Morphine hydrochloride
- 2.Methadone
- 3.Pethidine (Meperidine)
- 4.Trimeridine (Promedol)
- 5.Fentanyl

**Partial agonists** (*have affinity for binding but low efficacy*)

- 1.Codeine phosphate
- 2.Hydrocodone
- 3.Propoxyphene
- 4.Butorphanol

**Agonist-antagonist** (*produce an agonist effect at one receptor and an antagonist effect at another*)

- 1.Buprenorphine
- 2.Pentazocine
- 3.Nalorphine

**Antagonists** (*have affinity for binding but no efficacy; block action of endogenous and exogenous ligands*)

- 1.Naloxone hydrochloride
- 2.Naltrexone
- 3.Nalmefene

The ***abuse potential*** of opioid analgesics is determined by kinetic properties, because development of drug dependence is connected with rapid build-up of the brain concentration.

### **Mechanism of opioid analgesics (narcotic) action**

All drugs in the group of opioid analgetics act by binding to specific OR in the CNS due to their chemical resemblance with endogenous ligands. They produce effects that mimic the action of endogenous neurotransmitters, such as endorphins, enkephalins, and dynorphins. All drugs work as an agonist at antinociceptive system. Opioids interact stereospecifically with protein receptors on the membranes of certain cells in the CNS, on nerve terminals in the periphery, and on cells of the gastrointestinal (GI) tract and other anatomic regions. The major effects of the opioids are mediated by three major receptor families (Table 1).

**Table 1.****OPIOID RECEPTOR SUBTYPES AND EFFECT OF STIMULATION**

Receptor Subtypes	Effects
<b>μ-(mu) opioid receptor</b>	μ1 Analgesia μ1 Physical dependence
	μ2 Analgesia μ2 Physical dependence μ2 Respiratory depression μ2 Euphoria/sedation μ2 Reduced GI motility μ2 Pupil constriction
<b>δ-(delta) opioid receptor</b>	Analgesia Physical dependence Antidepressant activity Affective behavior Reinforcing actions Reduced GI motility
<b>κ-(kappa) opioid receptor</b>	Analgesia Sedation/ <b>dysphoria</b> Pupil constriction Inhibition of production of ADH Physical dependence

Opioids cause hyperpolarization of nerve cells, inhibition of nerve firing, and presynaptic inhibition of transmitter release. Morphine acts at κ-receptors in Lamina I and II of the dorsal horn of the spinal cord, and it decreases the release of substance P, which modulates pain perception in the spinal cord. Morphine also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

Each receptor family exhibits a different specificity for the drug it binds. The analgesic properties of the opioids are primarily mediated by the μ receptors; however, the κ receptors in the dorsal horn also contribute. For example, butorphanol and nalbuphine primarily owe their analgesic effect to κ-receptor activation. The enkephalins interact more selectively with the δ receptors in the periphery.

**THE PHARMACOLOGY OF MORPHINE**

The pharmacology of morphine described as prototype. Morphine is the major analgesic alkaloid contained in crude opium and it is the prototype of strong agonist. It has a high affinity for μ- receptors and varying affinities for δ- and κ-receptors.

## Pharmacokinetics

**Absorption** of morphine from the GI tract is slow and not complete. Significant first-pass metabolism of morphine occurs in the liver; therefore, intramuscular, subcutaneous, or IV injections produce the most reliable responses. When used orally, morphine is commonly administered in an extended-release form to provide more consistent plasma levels. Opiates have been taken for nonmedical purposes by inhaling powders or smoke from burning crude opium, which provide a rapid onset of drug action.

**Distribution.** Morphine rapidly enters all body tissues, including the fetuses of pregnant women, and should not be used for analgesia during labor. About 30% is bound to plasma proteins. Morphine freely crosses placenta and can affect the foetus more than the mother. Only a small percentage of morphine crosses the blood-brain barrier, because morphine is the least lipophilic of the common opioids. This contrasts with the more fat-soluble opioids, such as fentanyl, methadone, and heroin, which readily penetrate into the brain.

**Metabolism.** Morphine is conjugated in the liver to glucuronic acid. Morphine-6-glucuronide is an active metabolite (a very potent analgesic) which accumulates during chronic dosing and contributes to analgesia, despite its restricted passage across bloodbrain barrier. Another metabolite morphine- 3-glucuronide has neuroexcitatory property (less active). The conjugates are excreted primarily in the urine, with small quantities appearing in the bile. The duration of action of morphine is 4 to 6 hours when administered systemically to morphine-naïve individuals but considerably longer when injected epidurally, because its low lipophilicity prevents redistribution from the epidural space. Elimination is almost complete in 24 hours and morphine is noncumulative.

## Pharmacodynamics

The main target of morphine action is CNS. It has site specific depressant and stimulant actions in the CNS by interacting primarily with the  $\mu$ -opioid receptor as a full agonist. The depressant actions are:

- **Analgesia (relief of pain without the loss of consciousness).** Morphine is a strong analgesic. Opioids relieve pain both by raising the pain threshold at the spinal cord level and, more importantly, by altering the brain's perception of pain. Patients treated with morphine are still aware of the presence of pain, but the sensation is not unpleasant. However, when given to an individual free of pain, its effects may be unpleasant and may cause nausea and vomiting.

- **Sedation** is different from that produced by hypnotics. Drowsiness and indifference to surroundings as well as to own body occurs without motor incoordination, ataxia or apparent excitement (contrast to alcohol). Higher



doses progressively induce sleep and coma. Morphine has no anticonvulsant action, but, fits may be precipitated.

- **Euphoria.** Morphine produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the ventral tegmentum. Morphine has a calming effect; there is loss of apprehension, feeling of detachment, lack of initiative, limbs feel heavy and body weight, mental clouding and inability to concentrate occurs. In the absence of pain or apprehension, these are generally appreciated as unpleasant the normal people. However, patients in pain or anxiety, and especially addicts, perceive it as pleasurable floating sensation: refer it as high.

- **Temperature regulating centre** (in hypothalamus). It is depressed; hyperthermia occurs in cold surroundings.

- **Miosis.** The pinpoint pupil, characteristic of morphine use, results from stimulation of  $\mu$  and  $\kappa$  receptors. Morphine excites the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation to the eye. This is a central action; no miosis occurs on topical application of morphine to the eye. [NB! This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.].

- **Certain cortical areas and hippocampal cells.** Excitation is seen in an occasional individual. Muscular rigidity and immobility is consistently manifested at high doses (especially on i.v. injection): resembles catalepsy seen in rats and mice. The proconvulsant action has been ascribed to inhibition of GABA release by hippocampal interneurons.

- **Respiration.** Morphine causes respiratory depression in a dose dependent manner by reduction of the sensitivity of respiratory center neurons to carbon dioxide. This occurs with ordinary doses of morphine and is accentuated as the dose increases until, ultimately, respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdose.

- **Depression of cough reflex.** Morphine has antitussive properties. In general, cough suppression does not correlate closely with analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different from those involved in analgesia.

- **Vasomotor center.** It is depressed at higher doses and contributes into the fall in BP.

- **Emesis.** Morphine directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.

- **Vagal center.** It is stimulated so bradycardia is the usual response.

- **Autonomic nervous system.** Morphine causes mild hyperglycaemia due to central sympathetic stimulation. It has weak anticholinesterase action.

- **Hormonal actions.** Morphine inhibits release of gonadotropin-releasing hormone and corticotropin-releasing hormone, and it decreases the concentration of luteinizing hormone, follicle-stimulating hormone, adrenocorticotrophic hormone, and OI-endorphin. The sex hormone and cortisteroids levels are lowered. Morphine increases growth hormone release and enhances prolactin secretion. It increases antidiuretic hormone and, thus, leads to urinary retention.

- **Histamine release.** Morphine releases histamine from mast cells, causing urticaria, sweating, and vasodilation, and bronchoconstriction due to this bronchial asthma is contraindication for use of morphine.

- **GI tract.** Morphine decreases the motility and increases the tone of the intestinal circular smooth muscle. It also increases the tone of the anal sphincter. Morphine decreases GI secretions: reduction in transfer of water and electrolytes from mucosa to the lumen. Absorption of fluid is increased due to stasis. Overall, morphine produces constipation, with little tolerance developing. It can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

- **Cardiovascular system.** Morphine causes vasodilatation due to histamine release, depression of vasomotor centre, direct action decreasing tone of blood vessels.

Therapeutic doses cause little change in the BP, in higher doses BP is decreased. Postural hypotension and fainting do occur due to impairment of vascular reflexes. Morphine has little direct effect on heart; rate generally decreases due to stimulation of vagal centre, but may increase reflexly if the BP falls. Intracranial tension tends to rise as a consequence of CO<sub>2</sub> retention leading to cerebral vasodilatation and increasing the cerebrospinal fluid pressure.

- **Urinary bladder.** Tone of both detrusor and sphincter is increased leading to urinary urgency and difficulty in micturition. It inhibits the urinary bladder voiding reflex so catheterization may be required. Contractions of ureter are also increased.

- **Uterus.** Morphine may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

## PECULIARITIES OF OTHER PREPARATIONS

### METHADONE

Methadone is a synthetic opioid that interacts with  $\mu$ - receptors. The analgesic activity of methadone is equivalent to that of morphine. Metadone has similar actions to morphine. The miotic and respiratory-depressant actions of methadone have average half-lives of 24 hours.

- **Pharmacokinetics.** Methadone is well-absorbed when administered orally, in contrast to morphine, which is only partially absorbed from the GI tract, so it can be given orally. It accumulates in tissues on repeated

administration, where it remains bound to protein, from which it is slowly released. Plasma protein binding is 90% and it is metabolized in liver, primarily by demethylation and cyclization. Metabolites are excreted in urine. It has a somewhat longer duration of action (4–6 hours).

### CODEINE

Codeine is present in crude opium in lower concentrations and is inherently less potent. It's a much less potent analgesic and greater antitussive action than morphine, but has a higher oral effectiveness. It shows good antitussive activity at doses that do not cause analgesia. Codeine exerts sedative effect and potentiates the action of other sedative drugs and analgesics.

**Pharmacokinetics.** Codeine is well absorbed when taken orally. A single oral dose acts for 4-6 hours. It is methyl-morphine, occurs naturally in opium, and is partly converted in the body to morphine.

### PETHIDINE (MEPERIDINE)

Meperidine is a synthetic opioid structurally unrelated to morphine that binds to opioid receptors, particularly  $\mu$ - receptors. However, it also binds well to  $\kappa$ -receptors. Analgesic efficacy approaches to morphine. It does not effectively suppress cough. Meperidine causes a depression of respiration similar to that of morphine, but it has no significant cardiovascular action when given orally. On IV administration, meperidine produces a decrease in peripheral resistance and an increase in peripheral blood flow, and it may cause an increase in cardiac rate (due to antimuscarinic action). Meperidine like morphine dilates cerebral vessels, increases CSF pressure, and increase in tone of smooth muscle but constipation and urinary retention are less prominent. Meperidine does not cause pinpoint pupils but, rather, causes the pupils dilation due to atropine-like action.

**Pharmacokinetics.** Meperidine is well absorbed from the GI tract, and is useful when an orally administered potent analgesic is needed. Pethidine is nearly completely metabolized in liver. It is N-demethylated to normeperidine in the liver and is excreted in the urine. However, meperidine is most often administered parenterally. The drug has a duration of action of 2 to 4 hours, which is shorter than that of morphine.

### FENTANYL

Fentanyl, which is chemically related to meperidine, has 100-fold the analgesic potency of morphine and is used in anesthesia. It is administered IV, IM, epidurally, or intrathecally.

Fentanyl is often used during cardiac surgery because of its negligible effects on myocardial contractility. Muscular rigidity, primarily of the abdomen and chest wall, is often observed with fentanyl use in anesthesia.

**Pharmacokinetics.** The drug is highly lipophilic and has a rapid onset (1–3 min) and short duration of action (15 to 30 minutes). Fentanyl is metabolized to inactive metabolites by the cytochrome system, and drugs that inhibit this isozyme can potentiate the effect of fentanyl. Most of the drug and metabolites are eliminated through the urine.

### **TRIMEPIRIDINE (PROMEDOLUM)**

It is a synthetic preparation with a structure unrelated to morphine. It is administered orally, SC, IM, IV; begins to act in 10 min after IV administration and acts during 3–4 hrs.

It exceeds analgesic activity of morphine 2–4 times; causes less inhibition of the respiratory center, less stimulation of the n.vagus and emetic center; has spasmolytic action on the GI tract; stimulates uterus contractions without a negative influence on the fetus.

### **PENTAZOCINE**

Pentazocine is a synthetic preparation that acts as an agonist on  $\kappa$ -receptors and is a weak antagonist at  $\mu$ - and  $\delta$ -receptors and also binds to  $\sigma$ -receptors those results in dysphoria (agonist-antagonist). It may be administered orally, SC, IM, IV, or rectally; acts during 3–4 hrs.

Pentazocine promotes analgesia by activating receptors in the spinal cord ( $\kappa_1$ -). It is used to relieve moderate pain; may be used in children and for analgesia in labor. Pentazocine produces less euphoria compared to morphine. In higher doses, the drug causes respiratory depression and decreases the activity of the GI tract ( a decrease in the activity of the gut), nausea, vomiting, vertigo, sweating, hyperemia of skin, rises BP and can cause hallucinations, nightmares, dysphoria, tachycardia, and dizziness. The latter properties have led to its decreased use. In angina, pentazocine increases the mean aortic pressure and pulmonary arterial pressure and, thus, increases the work of the heart. The drug decreases renal plasma flow. Tolerance and dependence develop on repeated use.

### **OTHER ANALGESICS**

#### **TRAMADOL**

Tramadol is a centrally acting synthetic analgesic that binds to the  $\mu$ -OR. In addition, it weakly inhibits reuptake of norepinephrine and serotonin that leads to the reinforcement of spinal inhibition of pain impulses. Tramadol has a mixed mechanism of action (opioid + non-opioid). It acts during 3–6 hrs. Its respiratory-depressant activity is less than that of morphine.

It is **indicated** for mild-to-moderate short-lasting, acute and chronic pain. Naloxone can only partially reverse the analgesia produced by tramadol

or its active metabolite. The drug undergoes extensive metabolism, and one metabolite is active.

**Side effects** are vertigo, nausea, headache, sleepiness, sweating, lowering of BP, tachycardia, and dry mouth. Anaphylactoid reactions have been reported; seizures that can occur, especially in patients taking selective serotonin reuptake inhibitors, tricyclic antidepressants, or in overdose. Tramadol should also be avoided in patients taking monoamine oxidase inhibitors.

### THERAPEUTIC USES OF OPIOID ANALGESICS

- **Severe pain.** Despite intensive research, few other drugs (trimeperidine, meperidine) have been developed that are as effective as morphine in the relief of pain. Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, opiates may be used to supplement the sleep-inducing properties of benzodiazepines, such as temazepam.

- **Acute pulmonary edema.** Intravenous (IV) morphine dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure by its vasodilatory effect and decrease in pulmonary vessels resistance.

- **Myocardial infarction** (Trimeperidine, morphine, fentanyl).

- **Preanaesthetic medication** (meperidine).

- **Neuroleptanalgesia** (fentanyl).

- **Diarrhoea.** Morphine decreases the motility and increases the tone of intestinal circular smooth muscle, but for treatment of diarrhoea other opioid agonist that lacks of analgesic effect (loperamide is used).

- **Cough:** Morphine suppresses the cough reflex but as antitussive codeine is used.

- **Painfull labor.** Trimeperidine stimulates uterus contractions without a negative influence on the fetus. Meperidine has significantly less effects on uterine smooth muscle than morphine and is the opioid commonly employed in obstetrics and its shorter action and different route of metabolism; fentanyl, pentazocine).

- **Cardiac surgery** fentanyl is often used because of its negligible effects on myocardial contractility.

- **Controlled withdrawal** of dependent abusers from heroin and morphine (Methadone). The patient is then slowly weaned from methadone. It causes a withdrawal syndrome that is milder but more protracted (days to weeks) than that of other opioids.

### ADVERSE EFFECTS

- **Sedation,** mental clouding, lethargy and other subjective effects which may even be dysphoric in some subjects.

- **Vomiting** (occasional in recumbent patient).
- **Constipation** (common).
- **Respiratory depression.** Severe respiratory depression occurs and can result in death from acute opioid poisoning. A serious effect of the drug is stoppage of respiratory exchange in patients with emphysema or cor pulmonale.
  - **Blurred vision.**
  - **Acute urinary retention** in benign prostatic hyperplasia.
  - **Hypotension.** BP may fall especially in hypovolaemic patient and if he/she walks about, but pentasocin causes increase BP.
  - **The elevation of intracranial pressure** (particularly in head injury, can be serious).
  - **Enhancement of cerebral and spinal ischemia** (morphine).
  - **Allergy** (uncommon) and anaphylactoid reaction is rare. Urticaria, itch, swelling of lips are the manifestations.
  - **A local reaction at injection** may occur due to histamine release/
  - **Tolerance and physical dependence.** Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of morphine. Physical and psychological dependence readily occur with morphine and with some of the other agonists to be described.
  - **Withdrawal** produces a series of autonomic, motor, and psychological responses that incapacitate the individual and cause serious almost unbearable symptoms. However, it is very rare that the effects are so profound as to cause death. (Detoxification of heroin- or morphine-dependent individuals is usually accomplished through the oral administration of methadone, buprenorphine, or clonidine). Withdrawal of morphine is associated with marked drug-seeking behaviour. Physical manifestations are-lacrimation, sweating, yawning, anxiety, fear, restlessness, gooseflesh, mydriasis, tremor, insomnia, abdominal colic, diarrhoea, dehydration, rise in BP, palpitation and rapid weight loss. Delirium and convulsions are not a characteristic feature (contrast to barbiturates) and are seen only occasionally. Cardiovascular collapse and fatality are rare if supportive measures are instituted. Opioid antagonists (naloxone, nalorphine) precipitate acute withdrawal syndrome in the dependent subject. In the more severely dependent, even 0.2 mg of naloxone can precipitate marked withdrawal that can be used for diagnosis of drug dependence.

**Treatment** consists of withdrawal of morphine and substitution with oral methadone (long-acting, orally effective) followed by gradual withdrawal of methadone.

## CONTRAINDICATIONS

1 Infants and the elderly, so as they are more susceptible to the respiratory depressant action of morphine.

2. Respiratory insufficiency (emphysema, pulmonary fibrosis, cor pulmonale), sudden deaths can occur.
3. Bronchial asthma, COPD. Morphine can precipitate an attack by its histamine releasing.
4. Severe brain injury (morphine).
5. Hypotensive states and hypovolaemia (morphine).
6. Undiagnosed acute abdominal pain. Morphine can aggravate certain conditions, e.g. diverticulitis, biliary colic, pancreatitis. Inflamed appendix may rupture. Morphine can be given after the diagnosis is established.
7. Elderly male (chances of urinary retention are high)
8. Hypothyroidism, liver and kidney disease. Such patients are more sensitive to morphine.
9. Unstable personalities (are liable to continue with its use and become addicted).

### **ACUTE MORPHINE POISONING**

Stupor or coma, flaccidity, unconsciousness, cyanosis, pinpoint pupil, the abolish of reflexes, abnormal muscular tone, bradycardia, fall in BP and shock, Chain-Stocks' breath, the urinary retention, spasm of the intestine and bowel. Convulsions may occur in morphine poisoning. Death is due to respiratory failure. The human lethal dose is estimated to be about 250 mg.

**Emergency help.** The gastric lavage with 0,5% solution of potassium permanganate. Being basic drug it is partitioned to the acid gastric juice, ionizes there and does not diffuse into blood. Specific antidote: naloxone (an antagonist of narcotic analgesics) 0.4–0.8 mg IV. Repeted every 2–3 min till respiration picks up. Alropine (for a decrease in the vagal action of morphine).

### **ANTAGONISTS**

The opioid antagonists bind with high affinity to OR but fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in normal individuals. However, in patients dependent on opioids antagonists rapidly reverse the effect of agonists, such as heroin, and precipitate the symptoms of opiate withdrawal.

### **NALOXONE**

Naloxone is a synthetic preparation that used to reverse the coma and respiratory depression of opioid overdose. Naloxone is a competitive antagonist at  $\mu$ -,  $\kappa$ - and  $\delta$ -receptors, with a 10-fold higher affinity for  $\mu$ -than for  $\kappa$ -receptors. This may explain why naloxone readily reverses respiratory depression with only minimal reversal of the analgesia that results from agonist stimulation of  $\kappa$ - receptors in the spinal cord. It rapidly displaces all receptor-

bound opioid molecules and, therefore, is able to reverse the effect of a heroin overdose. Within 30 seconds of IV injection of naloxone, the respiratory depression and coma characteristic of high doses of heroin are reversed, causing the patient to be revived and alert. Naloxone has a half-life of 60 to 100 minutes.

Naloxone produces no pharmacologic effects in normal individuals, but it precipitates withdrawal symptoms in opioid abusers.

**Indications.** Diagnosis of opioid dependence-precipitates withdrawal in dependent subjects. Naloxone is used in acute poisoning with narcotic analgesics. It also partially reverses alcohol intoxication. To reverse respiratory depression. Naloxone has been found to elevate BP in endotoxic or hypovolaemic shock, stroke and spinal injury.

### NALTREXONE

Naltrexone has actions similar to those of naloxone. It is metabolically more stable than naloxone and is taken orally. Naltrexone has a longer duration of action than naloxone, and a single oral dose of naltrexone blocks the effect of injected heroin for up to 48 hours. Naltrexone in combination with clonidine – and, sometimes, with buprenorphine – is employed for rapid opioid detoxification. It may also be beneficial in treating chronic alcoholism by an unknown mechanism; however, benzodiazepines and clonidine are preferred.

**Side effects** are nausea and headache; high doses can cause hepatotoxicity.

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*Навчальне видання*

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з англійською мовою навчання***

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