Opiate Toxicity

Presented

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Narcotic Analgesics

- It relieve pain, induce sleep, insensibility, and conscious level alteration. It is classified into five types:-

1- First type (Phenanthrene opium alkaloids)

A-Phenanthrene group : Morphine and codeine (methyl morphine),

B- Benzylisoquinoline group : Papaverine and narcotine.

2- Second type (Semi-synthetic morphine derivatives)

Heroin (diacetylmorphine), ethyl morphine, dihydromorphinone.

3- Third type (Synthetic morphine-like agonists)

Meperidine (pethidine), fentanyl, methadone.

4- Fourth type (Mixed agonist-antagonists)

Pentazocine, buprenorphine, nalbuphine, and butorphanol.

5- Fifth type (Narcotic antagonists)

Naloxone (Narcan), naltrexone, nalorphine, and levallorphan.

Opiate

Opiate is one of narcotic analgesic drugs, it divides into two types:-

1- First type

- It is natural opiate, derived from dry secretions of poppy capsule that contains opiate alkaloids such as codeine, noscapine, papaverine, and morphine

2- Second type

- It is synthetic opiate that has similar chemical structure.
- Morphine and heroin are the most common opiate abused.
- Opiate may be administered by oral, parenteral, and inhalation routes.
- Maximum toxic and therapeutic effects appear after:-

10/M of IV - 30/ M of IM - 90/M of subcutaneous or oral administration.

- Opiate is rapidly metabolized in liver, so it has short duration of action even in overdose.
- It is not stored in body tissues because it is excreted in urine.
- But, buprenorphine and propoxyphene have a prolonged action in overdose because it is fat-soluble.

Opiate Receptors

- It is related to mechanism of opiate action.

1- Mu receptors: found in brain (medulla, limbic system, medial thalamus, sensory area) and are stimulated by morphine.

It is divided into Mu1 and Mu2:-

A- Mu1 is responsible for GIT symptoms and euphoria.

B- Mu2 is responsible for miosis, spinal analgesia, and respiratory depression.

2- Kappa receptors: found in brain and spinal cord.

- It is responsible for agonist-antagonists action, miosis, and spinal analgesia.
- It is divided into K1, K2, and K3.

3- Sigma receptors: responsible for side effects of agonist-antagonists (hallucination and dysphoria), but their sites of location are unknown.

4- Delta and Zeta receptors: unknown role.

- There are endogenous opiates (peptides) such as methionine, enkephalin, leucine, dynorphin, and B-endorphin that have role in addiction, tolerance, and pain modulation.
- The addicted person can develop tolerance to all morphine effects except miosis and constipation.

Opiate Pharmacodynamics

- Opiate stimulates Mu receptors → activation of G proteins (G1, G2) → depression of adenyl - cyclase activity that is responsible for conversion of adenosine triphosphate (ATP) into adenosine monophosphate (AMP) →→ ↓ decrease in cyclic AMP level and then neuron cells activity.
- It causes opening of potassium channel →→ ↑ increase of conduction within it →→ ↓ decrease of neuron cells activity.
- It causes closure of the calcium channel and ↓ decrease of neurotransmitter release at same time →→ ↓ decrease of neuron cells activity also.

Cont.

- Opiates affect on functions of different body systems.
- Opiates have many stimulation and depression effects on CNS.
- **Depression effects:** Analgesia (euphoria), narcosis, respiratory and cough depression, inhibition of polysynaptic spinal reflexes, and hypothermia .
- **Stimulation effects:** Vomiting, miosis, release of anti-diuretic hormone (ADH), stimulation of cardio-vagal center and monosynaptic spinal reflexes.
- High dose leads to hypotension because of vasomotor depression and histamine release that lead to peripheral vasodilatation and sweating.
- Opiate has a spasmogenic effect leading to constipation.
- It leads to urinary retention because of depressed micturition reflex, an increase of anti-diuretic hormone (ADH) secretion, and internal sphincter spasm. It decreases basal metabolic rate.

Clinical Picture of Acute Opiate Overdose

- Clinical picture of acute opiate overdose are exaggerated manifestations of opiate clinical use.

- **Miosis**
- It is due to stimulation of Edinger-Westphal nucleus
- Meperidine (pethidine) is only one of opiates that cause pupil dilatation.
- Pupil dilatation in some cases of opiate overdose if it is associated with hypoxia or ingestion of non-opiate drugs.
- **Cyanosis (Respiratory depression)**
- It depresses sensitivity of respiratory center for arterial co^2 level →decrease rate of respiration, not its depth inducing respiratory depression (cyanosis).
- Hypoxia is the cause of death in these cases.
- Respiratory depression induces death based on opiate dose and patient tolerance.
- Some patients take low dose of opiate, but they haven't tolerance, so death may have occurred.
- Other patients take large dose of opiate, but they have a tolerance, so death may not have occurred.

Clinical Picture of Acute opiate overdose (Cont.

- **Non-cardiac pulmonary odema**
- It causes hypoxia → pulmonary vasoconstriction and elevated pulmonary capillary pressure →→ protein-rich fluid leakage into interstitial tissue and alveoli → pulmonary odema.
- Clinical picture of pulmonary odema is rales, wheeze, rhonchi, and pink, frothy sputum.
- **Nausea and vomiting**
- It is due to initial stimulation of chemoreceptor's trigger zone, but this zone has not any response to further stimulus neither opiate additional doses nor from any emetic such as ipecac.
- So, ipecac has not any role in opiate intoxication although it acts centrally within 15 to 30 /m in normal conditions.

❑ If pure heroin is taken by persons who have not been accustomed to it, death may occur.

❑ Therapeutic dose of opiate do not cause pulmonary odema,

❑ But, overdose may cause non-cardiac pulmonary odema.

Clinical Picture of Acute opiate overdose (Cont.

- **CNS depression and then euphoria**
- **Drowsiness and coma** follow CNS excitatory phase.
- **Seizures**

- Common in children opiate overdose due to CNS excitation.

- It is not common in adult opiate overdose.

- Meperidine and propoxyphene overdose →**Seizures.**

- **Urinary retention and constipation**

hypertonia and decrease of muscle contractions leading to sphincter spasm.

- **Orthostatic hypotension** (peripheral vasodilatation)
- **Supine hypotension** (associated drugs intake, severe uncorrected hypoxia, or hypovolemia)

Clinical Picture of Acute opiate overdose (Cont.

- Opiate overdose administration may be:-

A. Oral

B. Parenteral inducing:-

- Itching, urticaria, and flush skin due to histamine release.
- Track marks, sclerotic veins, atrophic depressed scars of skin, puffy hands and feet because of venous insufficiency and lymphatic obliteration.
- Track marks indicate fresh injection sites.

Complications of Opiate Abuse

- **Infection:** AIDs, hepatitis, abscess, tetanus, endocarditis, and bacterial sepsis.
- **Pulmonary:** Pneumonia, pulmonary odema, pulmonary embolism, atelectasis, and lung fibrosis.
- **Skin** : Abscess, cellulitis, phlebitis, lymphangitis, and scars
- **Neurologic:** Polyneuritis, transverse myelitis, cerebral odema, and horner syndrome
- **Hepatic**: Hepatitis and liver cirrhosis
- **Glomerulonephritis**
- **Hematologic** : Leucopenia, thrombocytopenia, and anemia
- **Immunological:** Elevated levels of IgM and IgG, decreased levels of C3 and total complement
- **Musculoskeletal:** Spondylitis and lumbar vertebral osteomyelitis
- **Gastrointestinal tract:** Chronic constipation

Treatment

- **Treatment depends on condition of patient, signs and symptoms.**

1- Life-saving measures (complicated and comatose cases)

A - Airway

clean airway (suction of secretions - removing any foreign bodies)

B- Breathing

humidified oxygen via face mask or nasal cannula for mild cases, or endotracheal intubation and ventilator in severe cases

C- Circulation (monitoring of blood pressure, pulse, heart)

2-Symptomatic treatment

- IV glucose 50% or 25% + Thiamine (B1) should be given in acute opiate overdose cases according to clinical condition of patient.

Antidote

Naloxone is considered specific opiate antidote.

- It has a high affinity for **Mu receptor** and reverses opiate effects that act on this receptor at **low doses**.
- Its affinity for **kappa and sigma receptors** is less and then **larger doses** of naloxone are required to reverse pentazocine (Talwin) overdoses and other drugs that bind these receptors.
- **Naloxone** reverses all pharmacological effects of opiates except **non-cardiac pulmonary odema** that needs more time (24 to 48 hours) for recovery because hypoxia is the cause of non-cardiac pulmonary odema not direct pharmacological effect of opiate.
- If there are persistent clinical and radiological lung abnormalities after 48 hours, it may be **aspiration pneumonia** that needs **antibiotics**.
- **Digitalis or diuretics** do not play any role in treatment of pulmonary odema in cases of opiate overdose.

Naloxone (CONT)

- **Routes** are IV, endotracheal, and sublingual.
- **Initial adult dose** is 0.4 mg to 2 mg IV (1 to 5 ampoules)
- Naloxone ampoule (Narcan) = 0.4 mg.
- **Maintenance dose** is 0.4 mg to 0.8 mg per hour (1 to 2 ampoules per hour).
- **Infusion dose** is 4 mg in 500 ml saline 0.9% or in glucose 5% according to signs and symptoms of patient.
- **Child dose** is 0.01 mg/kg or 0.1 mg /kg.
- Its effect appears after 2 to 3 /M from administration, it reaches peak within 5 to10 /M - half-life is 30 to 80 /M.
- Efficacy of naloxone (0.4 mg) persists for 45 minutes after IV administration.

Naloxone (CONT.)

- Some cases have not any response to IV administration of naloxone, so additional dose **(2mg)** should be given, and then it is repeated every five minutes until getting a response or reaching of naloxone maximum dose **10 mg** (25 ampoules).
- If there is not any response for naloxone after administration of its maximum dose **(10 mg),** this means that diagnosis is not opiate intoxication.
- If there is partial response to naloxone, case may be associated with mixed overdose or cerebral anoxia.
- Large doses of naloxone should be needed for reversing overdoses of codeine, propoxyphene, methadone, and agonist-antagonist drugs.
- After reversing opiate overdose via naloxone administration, we should observe patient for 12 to 24 hours after weaning of naloxone drip.

Side Effects of Naloxone

Hypertension

Naloxone release catecholamine and renin inducing hypertension

Seizures

Cerebral anoxia, infection, or trauma may be causes of seizures.

Vomiting

Emesis may occur immediately after naloxone injection.

Nalmefene

- It is new pure opiate antagonist that reverses opiate effects for longer periods than naloxone wherein its half-life is 10 to 12 hours.

For example:-

- 1 mg of nalmefene is given by IV, opiate effects will be reversed for 4 hours.
- 2 mg of nalmefene is given by IV, opiate effects will be reversed for 8 hours.
- 50 mg of nalmefene is given by oral, opiate effects will be reversed for 48 hours.

Gastrointestinal Decontamination

- It is carried out by **gastric lavage.**
- Cuffed endotracheal intubation should be used during lavage for comatose patient to prevent aspiration.
- **Ipecac** is **contraindicated** even if patient is conscious because chemoreceptor's trigger zone is depressed via opiate, it is stimulated initially but it is depressed later beside the possibility of seizures occurrence.
- **Repeated doses of activated charcoal** should be used after lavage because conjugated and unchanged opiates are excreted in bile and stomach by enterohepatic circulation of opiate apart from the route of opiate administration (oral or intravenous).

Abstinence Syndrome (Withdrawal Symptoms)

- It occurs after sudden cessation of opiate.
- Manifestations of different opiates' withdrawal are similar, but time course is different according to potency and duration of drugs.

Withdrawal symptoms of short-acting opiates:- Meperidine

- It appears after 3 to 4 hours and subside within 4 to 5 days after opiate cessation.

Withdrawal symptoms of long-acting opiates:- Methadone

- It appears after 2 days, subside after 2 weeks or more.

- Withdrawal symptoms severity is greatest in potent and short-acting opiates, but it is least in long-acting opiates.
- Withdrawal symptoms of agonist-antagonist (nalbuphine) are very mild.

Manifestations of Withdrawal Symptoms

It consist of four stages:-

1-First stage

It is drug craving and anxiety (persistent for 12 hours)

2- Second stage

Yawning, mydriasis, lacrimation, rhinorrhea, diaphoresis, tachycardia, hypertension, piloerection, and cold skin.

3- Third stage

Nausea, vomiting, diarrhea, abdominal pain, myalgia, muscle spasm, and twitching

4-Fourth stage

Fever, dehydration, hyperglycemia, spontaneous ejaculation, orgasm, and leucocytosis.

NOTES

- Manifestations of Opiate withdrawal are different from manifestations of alcohol withdrawal because it does not include delirium and seizures.
- Withdrawal manifestations appear after 5/M from starting point of treatment via naloxone and last for 1 to 2 hours.
- Withdrawal symptoms from discontinuity of repeated administration of naloxone may not occur.
- Neonatal narcotic abstinence syndrome may occur in newborn of an addicted mother.
- Neonatal narcotic abstinence syndrome is treated by clonidine (3 ug /kg/day).
- Lofexidine is considered an analogue of clonidine.

Mechanism of Withdrawal Symptoms

- Locus ceruleus nucleus is responsible for withdrawal symptoms because it has many opiates and α adrenergic receptors sites.

- Stimulation of opiate receptors via **morphine** and α adrenergic receptors via **clonidine** → → depression of adenyl-cyclase activity and ↓ decrease in cyclic AMP level.

- Opiate-addicted has physiological adaptation and normal level of adenyl-cyclase and cyclic AMP because of continuous stimulation.

- Discontinuous of opiate or replacement by antagonist administration (naloxone) leads to an acute rise of cyclic AMP level →↑increase in metabolic activity in neurons that correlates with clinical hyperactivity of withdrawing patient.

Treatment of Withdrawal Symptoms

- If opiate or α adrenergic receptor is again stimulated by **methadone** or **clonidine**, adenyl-cyclase activity will be decreased to normal level for the adapted cell, and patient will not be suffering from withdrawal symptoms,
- **Methadone** is treatment of abstinence symptoms besides non-opioid drugs such as **clonidine** to decrease withdrawal symptoms.
- Side effects of clonidine are **hypotension and sedation** that prevent the use of clonidine for addicted patient in outpatient clinic.
- Clonidine is an **antihypertensive** while naloxone is **hypertensive**.
- Clonidine **releases** endogenous opiate (B-endorphin) from brain stem and pituitary gland while naloxone **blocks** action of B-endorphin and then hypertension may occur.
- Action of clonidine can be reversed by naloxone administration.

Thank you