

## **PHARMACOLOGICAL ACTION OF MORPHINE EFFECTS**

**CNS** – Analgesic – Morphine relieves practically all forms of pain, but is more effective against dull, constant pain than against sharp episodes of pain. Morphine relieves pain by increasing the pain threshold (intensify the pain) and by altering reaction to pain, causing a state of euphoria and sedation (the pain is there but the individual bears the pain better),

**Respiration** – Acts centrally to stimulate respiration which is followed by depression.

**Vomition** – It acts as both emetic and anti-emetic. It causes nausea and vomition initially. Vomition following morphine administration only occurs in dog and cat which are the only species that respond to central acting emetics like morphine and apomorphine.

**Cough Reflex** – It depresses cough reflexes. Here codeine is preferred to prevent respiratory depression.

**Pupil (eye)** – It causes pupillary constriction in man and dogs while in animals in which morphine is excitatory e.g. cat, swine, goats, sheep, cattle and horses it produces pupillary dilation (Mydriasis). In the bird, the pupil is not affected because of non-responsive skeletal muscles.

**Spinal Cord** – Morphine although depresses the CNS, it stimulates the spinal cord. Therefore, morphine is strictly contra-indicated in strychnine poisoning.

**Cardiovascular system** – Morphine increases ventricular function in man and dog. This is due to the increased level of circulating catecholamines. Hypotension occurs following morphine administration. This occurs as a result of histamine release and depression of the vasomotor center. The cardiovascular function is unimportant when morphine is given therapeutic dosages. This is fortunate as the drug may be used to relieve pains of myocardial infarction and in management of pulmonary edema of cardiac origin.

## **THERMOREGULATOR CENTER**

Located in the hypothalamus is altered by morphine to the degree that generally lowers body temperature. The dog administered morphine shows signs of panting which later stops when body temperature is lowered. The cat responds similarly to dogs, but at higher doses, hyperthermia occurs and is maintained until morphine is completely metabolized. In horses, following morphine administration, sweating and hyperglycemia occurs as a result of increased circulating levels of epinephrine. In rabbits there is hyperthermia which may be related to increased levels of circulating catecholamines.

## **GIT**

Morphine increases the tone of the GIT smooth muscles decrease motility of the GIT. It also decreases hydrochloric acid secretion and delay the passage of gastric content. The biliary and pancreatic secretions are diminished, delaying digestion in the small intestine. It also decreased the propulsive peristaltic waves in the small intestine an colon. It produces in attention to normal sensory stimuli for the defecation reflex due to central action. Cause constipation.

## **SPECIES VARIATION**

**Dog:** Brief period of central excitement marked by restlessness, panting, salivation, nausea, vomiting urination and defecation. This is then followed by depression.

**Cat:** Morphine causes excessive CNS stimulation in the Cat. This excitation is thought to be due to the release of dopamine and norepinephrine in the brain. Drugs that depletes, norepinephrine (renorpine, tetrabenzaine) and those that block dopamine receptors (Chlorpromazine, haloperidol) in the brain can prevent this excitation.

**Horse:** Cattle, Goats, Swine, Ass are all excited by morphine. The mechanism is probably similar to what occurs in the cat.

## **ABSORPTION, FATE AND EXCRETION**

Morphine is absorbed rapidly from the small intestine and after injection. The major pathway for biotransformation is conjugation with glucuronic acid, then excreted by the kidney. The cat is deficient in this conjugation pathway lacking glucuronyl transferase enzyme. Hence, the half life of morphine is longer in cat.

Morphine is distributed in the kidney, liver, spleen and lung.

## **Contraindications**

- Acutely, uromic and toxemic patients.
- Strychnine poisoning
- Tetanus
- Epileptic patients.
- Cardiovascular check.
- Hypotensive patients.

- Acutely Asthmatic patients

## **MORPHINE DERIVATIVES**

**Codeine (Methylmorphine)** – is an important analgesic and antitussive drug. Used to allay irritating coughs in dogs. In therapeutic doses, it is less sedative an analgesic than morphine, but tolerance to the drug develops slowly and codeine is less addictive than morphine. It has less effect on the GIT and urinary tracts and on the pupil and causes less nausea and constipation than morphine. Codeine administered orally is not as effective an analgesic as when it is injected subcutaneously. Codeine is partly demethylated to morphine in the body and is partly changed to norcodeine. The conjugated forms of these compounds are excreted in the urine.

**Dihydromorphine (Dilaudid)** – is 5 times more potent than morphine in causing analgesia. Ha a greater respiratory depressant effect than morphine, although it may be less nauseating and constipation has been used in dogs and cats.

**Etorphine Hydrochloride (M-99)** – is 10,000 times as potent as morphine as an analgesic. Used mainly in wild and exotic animals.

**Oxymorphone HCL (Numorphan)** – is 10 times more potent than morphine as an analgesic has been used in dogs and cats.

### **Morphine Substitute**

Meperidine HCL (pethidine, demerol, dolantin). This is a non-morphine derivative. It has spasmolytic, analgesic and sedative activity.

### **Administration**

**I.M.** is the best route for administration. Local irritation and pain result from subcutaneous route. In cat, irritation and salivation occur when meperidine contacts buccal mucosa, and following I.M. and S. C. administration in cat emesis does not occur, but defecation occurs in some animals. Oral administration is not advised in large animals because of cost.

## **METABOLISM AND FATE**

Meperidine is absorbed following S.C., I.M., or oral administration. It has short duration of action (2 hours). It is inactivated in the liver by demethylation, though small amount is excreted unchanged in the urine.

## **PHARMACOLOGICAL EFFECTS**

**Thermoregulatory center** – it produces hypothermia response following S. C. injection. This response may be related to the stimulation of dopamine receptor in the brain.

**Cardiopulmonary effect** – it slows down the heart rate and causes a fall in blood pressure in dogs following I.M. injection. Intravenous doses of 0.05mg/kg produce broncho-constriction. At 2.5mg/kg, lung capacity decrease by 22%. The above response is probably due to a central vagal effect and the release of histamine.

**Analgesic Effect** – Its analgesic action is between morphine and codeine. In dogs, cough reflexes is depressed satisfactorily.

**Spasmolytic action or Effect on GIT** – its spasmolytic action is less than that of morphine. Meperidine relax, the intestine, the bronchi, the ureter and the uterus slightly. Meperidine has the advantage over morphine in that it can produce analgesia before inhibiting the body, including the placental and fetal tissues, and is used to allay parturition pains in women because it does not depress fetal respiration.

## **Toxicity**

It causes excitement and convulsing in cats when given subcutaneously in excess of 10-15mg per pound. This convulsion can be controlled by barbiturate administration. Meperidine potentiates the depressant effect of the barbiturates upon respiration. Nalorphine is an antagonist of the respiratory depressant and toxic effects of meperidine. Because meperidine is rapidly metabolized in cumulative toxicity is observed, but doses up to 6 times therapeutic dose causes anorexia and weight loss.

## **Clinical Uses.**

- Relieves pain
- Proanaesthetic medication.
- It can be used for the treatment of equine colic especially acute spasmodic condition.
- In cattle, it is used for calving to calm the nervous heifer and to provide analgesia during parturition.

### **Methadone (Dolophine)**

This synthetic substance that has many of the properties of morphine including addiction in man. It is a good analgesic but produces respiratory depression. It is used in the relief of pain, treatment of narcotic abstinence syndrome and treatment of heroine users.

**Phentanyl (R-4263; Fentanyl)** – This is an analgesic agent whose potency is about 100 times more than that of morphine and 1000 times more than that of pethidine. It has been used to produce complete surgical anaesthesia in dogs but is usually given with a neuroleptic in neuroleptanal gesia. Fentanyl reduces sensitivity to pain in all animals and causes respiratory depression which can be counteracted with nalophine. In dogs, rats and primates it induces sedation and myosis but in horses, mice and cats it is said to produce excitement and mydriasis. Phentanyl mixed with neuroleptics have certain advantages:

- Case of administration
- Wide safety margin
- Quite post-operative recovery
- Easily reversible with narcotic antagonists
- Well tolerated by patients or animals in poor physical condition.

### **Narcotic Antagonist**

In veterinary practice, the once of relevance are:

- Nalorphine
- Naloxone
- Diprenorhine

They are called opiod antagonist. They block effect of opiate receptors displacing narcotic molecules already present.

It is a morphine derivative.

### **Administration**

S.C., I.M. or I.V.

### **Absorption and Fate:**

It is readily absorbed fully by Git and metabolism of nalophine is by conjugation of the liver.

## **Action**

In the presence of narcotics, it has antagonistic effect.

- In the absence of morphine, it has C.N.S. depressant and analgesia.
- It does not antagonize mild respiration depressant.
- It does not cause constipation.
- It is a drug of choice for fetal respiratory depression of morphine in pregnant is antagonized without any effect on uterine motility, labour or incidence of still birth.
- It has typical withdrawal symptom in morphine addictive subjects.

## **Effect on Morphine Toxicity**

1. Counteract sedation and respiratory depression of morphine which usually cause restlessness is counteracted after administration of Nalorphine.
2. If first dose of Nalorphine fails additional dosages is contra-indicated.
3. Over doses of Nalorphine is treated by supporting respiration.

**Dosage** is 1mg for every 10mg of morphine or 20 mg of meperidine.

10 – 20mg to 1mg of etorphine.

## **Naloxone HCL**

- It has potency for 10-30 times that of nalorphine.
- It does not produce respiratory depression which occurs with other narcotic antagonists.

## **Action**

- It antagonizes respiratory depression caused by morphine, meperidine, oxymorphone.
- It does not antagonize the effect of inhalant anaesthetics, barbiturates, procaine or tranquilizers.
- The drug would also reverse the narcotic effect of fentanyl.

## **Administration**

It could be administered by all parental router however I.V. route is preferred for immediate effect.

## **Dosage**

For reversal of respiratory depressant effect of narcotic in dog these dosage are recommended. 0.1mg of naloxone for 1.5mg of oxymorphone 0.016 – 0.1mg of naloxone for 0.02 – 0.03mg fentanyl. 0.016 – 0.1mg of naloxone for 0.5mg of morphine.

## Diprenorphine

- Like nalorphine, it has antagonistic effect and may depress.
- It counteracts depression caused by morphine.
- This agent at twice the dose level of etorphine is capable of immobilizing wild animals.
- Precaution for its administration is same as nalorphine.
- This agent is used mainly in wild and exotic animals to specifically reverse the effect of etorphine.

**Route of Administration** - I.M. or I.V.

**Dosage** - 30mg/kg

## NON-NARCOTIC ANALGESIC DRUGS

