Analgesic and antipyretic drugs(Narcotics)

Pharmachemistry II, D.Pharm, Part 2

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Opioid/Narcotic Analgesics

" Narcotic analgesics in an old term for opioid analgesics. They are pharmacologically similar to morphine which is obtained from opium (Poppy plant) and they act on opioid receptor".

Mechanism of Action

- Opioids agonists bind to opiate receptors in the CNS to alter the perceptions of an emotional response to pain. They produce analgesia by:

1. Elevating pain perception threshold.
2. Changing the pain reaction. (i.e. even in the presence of pain patient does not bother about pain).
3. Production or induction of sleep.

Drug Examples and dosages

S. no.	Drugs	Doses
	Natural Alkaloids	
1	Morphine	15-30mg orally/2.5-5mg injected
2	Codeine	15-30mg orally SOS
	Synthetic compounds	
3	Pethidine	25-100mg/IM/SC SOS
4	Methadone	2.5-10mg orally/SC/IM 6hrly
5	Pentazocine	30-60mg IM/IV/SC
6	Fentanyl	25mcg patch

continued

S. no.	Drugs	Doses
Semi synthetic morphine derivatives		
7	Heroin (Diamorphine)	100mg injection IV
Other opioid Analgesics		
8	Butorphenol	1-4mg IM/IV
9	Tramadol hydrochloride	50-100mg TDS orally/IM/IV
10	Naloxone	0.4-2mgIM/IV/SC

Indications/Uses

- To treat pain that is unresponsive to non opioid analgesics.
- Adjuncts to anesthesia.
- Used to relieve cough.
- MI pain.
- In the treatment of diarrhea.

Contraindications / precautions

- Use cautiously in patients with head injury, hepatic or renal disease.
- Cautiously in CNS depression and in pregnant and breast feeding women.
- Use cautiously in elderly or debilitated patients who may need decreased dosage.

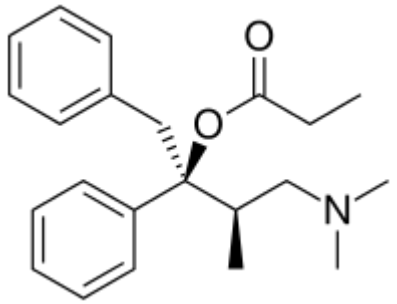
Adverse effects

- Sedation.
- Constipation.
- Hallucination.
- Respiratory Depression.
- Dizziness.
- Dysphonia.
- Orthostatic hypotension.
- Physical dependence.
- Psychological Dependence.

Drug interactions

- Simultaneously use with alcohol, antihistamines, hypnotics or sedatives causes additive CNS Depression.
- Concurrently use with non opioid analgesics may enhance pain relief.

Dextropropoxyphene is an analgesic in the opioid category, patented in 1955 and manufactured by Eli Lilly and Company. It is an optical isomer of levopropoxyphene. It is intended to treat mild pain and also has antitussive (cough suppressant) and local anaesthetic effects. The drug has been taken off the market in Europe and the US due to concerns of fatal overdoses and heart arrhythmias.Its onset of analgesia (pain relief) is said to be 20–30 minutes and peak effects are seen about 1.5–2.0 hours after oral administration.



Dextropropoxyphene - Alpha-d-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol propionate

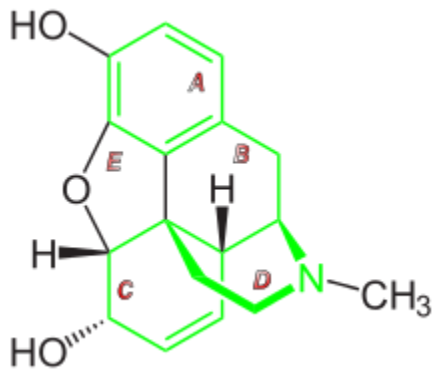
- Dextropropoxyphene, like codeine, is a weak opioid, known to cause dependency among recreational users
- Dextropropoxyphene has been found to be helpful in relieving the symptoms of restless legs syndrome
- In pure form, dextropropoxyphene is commonly used to ease the withdrawal symptoms in people addicted to opioids. Being very weak in comparison to commonly abused opioids, dextropropoxyphene can only act as a "partial" substitute. It does not have much effect on mental cravings, but it can be effective in alleviating physical withdrawal effects, such as muscle cramps.

Morphine is a pain medication of the opiate family which is found naturally in a number of plants and animals, including humans. It acts directly on the central nervous system (CNS) to decrease the feeling of pain.It can be taken for both acute pain and chronic pain.

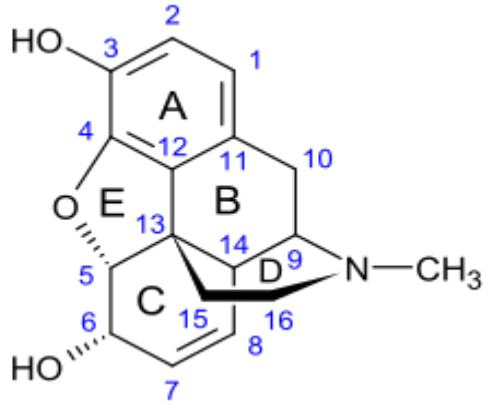
The primary source of morphine is isolation from poppy straw of the opium poppy.In 2013, approximately 523 tons of morphine were produced. Approximately 45 tons were used directly for pain, a four-fold increase over the last twenty years.Most use for this purpose was in the developed world. About 70 percent of morphine is used to make other opioids such as hydromorphone, oxymorphone, and heroin.It is a Schedule II drug in the United States, Class A in the United Kingdom,and Schedule I in Canada. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.Morphine is sold under many trade names. In 2016, it was the 158th most prescribed medication in the United States, with more than 3 million prescriptions.

Morphine is a benzylisoquinoline alkaloid with two additional ring closures.

- A rigid pentacyclic structure consisting of a benzene ring (A), two partially unsaturated cyclohexane rings (B and C), a piperidine ring (D) and a tetrahydrofuran ring (E). Rings A, B and C are the phenanthrene ring system. This ring system has little conformational flexibility...
- Two hydroxyl functional groups: a C3-phenolic [hydroxyl group] and a C6-allylic [hydroxyl group],An ether linkage between C4 and C5, Unsaturation between C7 and C8,A basic, [tertiary]-amine function at position 17, and Five centers of chirality (C5, C6, C9, C13 and C14) with morphine exhibiting a high degree of stereoselectivity of analgesic action.
- Morphine and most of its derivatives do not exhibit optical isomerism, although some more distant relatives like the morphinan series (levorphanol, dextorphan and the racemic parent chemical dromoran) do, and as noted above stereoselectivity in vivo is an important issue.



Chemical structure of morphine.
The benzylisoquinoline backbone is shown in green.



Morphine structure showing its standard ring lettering and carbon numbering system.

Uses and derivatives

- Most of the licit morphine produced is used to make **codeine** by methylation.

- It is also a precursor for many drugs including **heroin** (3,6-diacetylmorphine), hydromorphone (dihydromorphinone), and oxymorphone (14-hydroxydihydromorphinone).

- Most semi-synthetic opioids, both of the morphine and codeine subgroups, are created by modifying one or more of the following:Halogenating or making other modifications at positions 1 or 2 on the morphine carbon skeleton.

- As a result of the extensive study and use of this molecule, more than 250 morphine derivatives (also counting codeine and related drugs) have been developed since the last quarter of the 19th century. These drugs range from 25% the analgesic strength of codeine (or slightly more than 2% of the strength of morphine) to several thousand times the strength of morphine, to powerful opioid antagonists, including naloxone (Narcan), naltrexone (Trexan), diprenorphine (M5050, the reversing agent for the Immobilon dart) and nalorphine (Nalline).

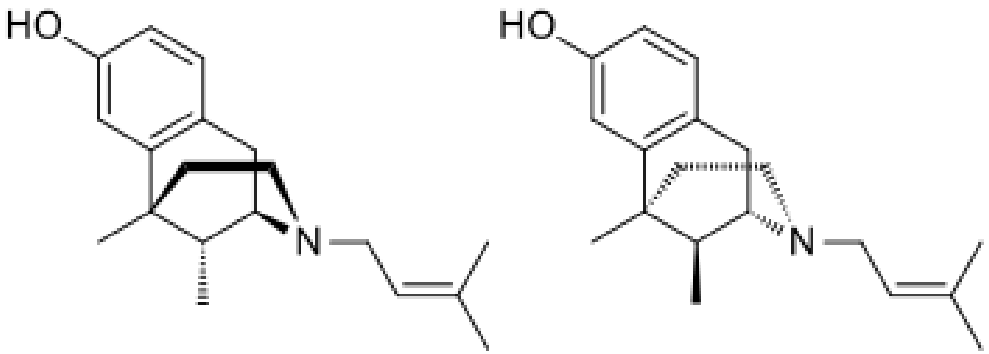
- Some opioid agonist-antagonists, partial agonists, and inverse agonists are also derived from morphine. The receptor-activation profile of the semi-synthetic morphine derivatives varies widely and some, like apomorphine are devoid of narcotic effects.

Opioids are substances that act on opioid receptors to produce morphine-like effects. Medically they are primarily used for pain relief, including anesthesia. Opioid receptors are a group of inhibitory G protein-coupled receptors with opioids as ligands

There are four major subtypes of opioid receptors.

Receptor	**Subtypes**	**Function**
delta (δ),DOR.OP1	δ1,[15] δ2	analgesia, antidepressant effects,convulsant effects,physical dependence may modulate μ-opioid receptor-mediated respiratory depression
kappa (κ),KOR,OP2	κ1, κ2, κ3	analgesia,anticonvulsant effects,depression,dissociative/hallucinogenic effects,diuresis,miosis,neuroprotection,sedation,stress
mu (μ),MOR,OP3	μ1, μ2, μ3	μ1:analgesia,physical dependence μ2:respiratory depression, miosis,euphoria, reduced GI motility, physical dependence μ3:possible vasodilation

Pentazocine, is an opioid analgesic used to treat moderate to severe pain. It is believed to work by activating (agonizing) κ-opioid receptors (KOR) and blocking (antagonizing) μ-opioid receptors (MOR). As such it is called an opioid as it delivers its effects on pain by interacting with the opioid receptors.



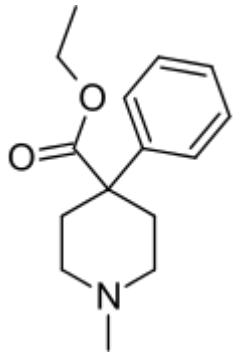
***(R)*-Pentazocine**

***(S)*-Pentazocine**

Pethidine, also known as meperidine is a synthetic opioid pain medication of the phenylpiperidine class.Pethidine is the prototype of a large family of analgesics including the pethidine 4-phenylpiperidines (piminodine, anileridine and others), the prodines (alphaprodine, MPPP, etc.), bemidones (ketobemidone, etc.) and others more distant, including diphenoxylate and analogues.

Pethidine is indicated for the treatment of moderate to severe pain, and is delivered as a hydrochloride salt in tablets, as a syrup, or by intramuscular, subcutaneous, or intravenous injection. For much of the 20th century, pethidine was the opioid of choice for many physicians; in 1975, 60% of doctors prescribed it for acute pain and 22% for chronic severe pain.

Compared with morphine, pethidine was thought to be safer, carry a lower risk of addiction, and to be superior in treating the pain associated with biliary spasm or renal colic due to its putative anticholinergic effects but it carries an equal risk of addiction, possesses no advantageous effects on biliary spasm or renal colic compared to other opioids, and due to its toxic metabolite norpethidine is more toxic than other opioids—especially during long-term use.The norpethidine metabolite was found to have serotonergic effects, so pethidine could, unlike most opioids, contribute to serotonin syndrome.



Pethidine

Assignment: Full Marks:10

(send it to : sefalihota@gmail.com)

For the following drugs:- Dextropropoxyphene,pentazocine,morphine,pethidine,codeine,methadone

1. Outline the pharmacological use and the common adverse drug reactions.
2. Categorize the drugs with their physical and chemical property
3. Recall the stability and storage conditions
4. Infer the official preparation of the specific drug of pharmaceutical use.
5. Make a table of physicochemical property, storage condition, official preparation and two brand names

Thank You