Isoquinoline Alkaloids

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Introduction...

Isoquinoline Alkaloids

Contains Isoquinoline nucleus

A number of therapeutically and socioeconomically important alkaloids like Morphine, Codeine, Papaverine, etc. are involved.
Introduction...

The therapeutic importance of these alkaloids ranges from narcotic-analgesics which are used for pain management in cancer and postoperative procedures to central muscle relaxant that are used in anesthesia to emetic agents used for poisoning.
Introduction...

-Misused among people worldwide

-Their production is regulated by the **International Agency of Narcotics (IAN)**
Subclasses of Isoquinolines

1. Morphinan class ex.: (Codeine, Morphine, Thebaine).

2. Benzyl isoquinoline class ex.: (Tubocurarine, Papaverine).
Subclasses of Isoquinolines...

3. Protoberiberine class ex.: (Beriberine).

4. Emetine class.
Subclasses of Isoquinolines...

5. Phthalide Isoquinololone class ex.: (Hydrastine).

6. Sanguinarine
Although these alkaloids share the same nucleus; but they show different pharmacologic activities...
Important alkaloids belong to this class...
Ipecac

(Emetine class),

*Cephaelis ipecacuanha*

(Brazilian)

*C. Acuminata* (Nicaragua)

(Fam: Rubiaceae)

The extract induces emesis through two mechanisms...
Pharmacognosy II

Alkaloids

Lec.: 3
It is used for gastric lavage in case of intoxications.

The plant contains two important alkaloids:-

1- Cephaeline in ration 2/3
2- Emetine in ratio 1/3

Its accumulation causes toxicity.
Emetine.HCl (inj.) has antiamoebic activity and indicated in amoebiasis as the main site of action is the GIT and Liver and in *Pyorrhea alveolaris*.
Tubocurarine

Soluble in water and insoluble in organic solvents.
an alkaloid from the bark and stems of *Chondrodendron tomentosum*; it is the active principle of curare;
It is also known as Indian arrow poison.

It is also extracted from stem, and bark of *Strychnus toxifera, S. castelnaei* (Fam: Loganinaceae).
It is a non-depolarizing neuromuscular junction receptor blocker (a competitive inhibitor to acetylcholine) causing flaccid paralysis.
Used for relaxation of skeletal muscles in:

1- Surgery

2- Strychnine poisoning

3- Neuropsychiatry

4- Myasthenia gravis (diagnostic)
Available as injection (Tubocurarine chloride), and its synthetic analogues:-

pancuronium, vecuronium, rocuronium, atracurium
Opium Alkaloids

Morphine
Opium alkaloids which belongs to the Morphinan class has important economic, political, medicinal, and sociological interest.
Opium was naturally grown in **Greece**, later has been cultivated in other areas around the world including India (for supplying Pharmaceuticals), Afghanistan, Turkey (for domestic uses), Iran, and China (for domestic uses).
Includes:

(Morphine, Codeine and Thebaine)

Extracted from the dried latex of poppy of the plant

Papaverum somniferum (Fam: Papaveraceae).
The plant has many species, and is of 15-60 cm height.

Collection...
Opium alkaloids have analgesic and narcotic action, frequent dosing causes physiologic and psychic dependence (addiction) and tolerance.
The Face of a Meth User – 10 years

Dead at age 38
Discovery of morphine

Morphine was discovered by *Freidrich Wilhelm Adam Serturner* (1783-1841)
In a series of experiments, performed in his spare time and published in 1806, he managed to isolate an organic alkaloid compound from the resinous gum secreted by *Papaver somniferum* -- the opium poppy.
He found that opium without alkaloid had no effect on animal models,

But the alkaloid itself had 10x the power of processed opium.

He named that substance morphine.
In 1818, French physician *Francois Magendie* published a paper describes how morphine cause pain relief and sleep to a patients.
This stimulated widespread medical interest.
At mid 1820s Morphine was widely available in Western Europe in standardized doses from several sources, including the *Darmstadt Chemical Company* started by Heinrich Emanuel Merck.
By the 1850s the injected morphine became a standard method of reducing pain during and after surgery.
Bayer began producing and marketing this drug as an analgesic and a "sedative for coughs" in 1898.
Because of its "heroic" ability to relieve pain, they called its derivative “heroin.”

The medical profession initially welcomed the new drug but soon recognized its addictive potential.
In 1913, Bayer halted production and focused on marketing their second blockbuster drug, Aspirin®.
Chemistry of Morphine
The biosynthetic pathway for the formation of morphine
SAR of Morphine
B-endorphin
Enkephalin
δ-receptor or delta - This receptor is widely distributed in the brain and also present in the spinal cord and digestive tract. Stimulation of this receptor leads to analgesic as well as antidepressant effects but may also cause respiratory depression.

<table>
<thead>
<tr>
<th>µ-receptors</th>
<th>K-receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia, Respiratory depression, Euphoria and dependance</td>
<td>Analgesia, miosis and sedation</td>
</tr>
<tr>
<td>Brain stem and thalamus</td>
<td>Limbic system, spinal cord</td>
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Effects on the body organs:-
Gastrointestinal tract

1. Constipation, is the most frequent side effect associated with long-term opioid therapy.

2. Nausea and vomiting.
On the eye

- Constriction of the pupils of the eye (miosis).
Kaolin and Morphine Mixture B.P.
Immune system

Morphine and its analogues suppress the adaptive immune system through inhibition of production of immune mediators.
The main pharmacological action of analgesics is on the cerebrum and medulla of the central nervous system

**Receptor Site:**

Opiate Receptors In The CNS

- Thalamus
- Hypothalamus
- Pituitary glands
- Periventricular nuclei
- periaquaductal grey
- RAPHE MAGNUS: Enkephalin (\(\delta\))
- \(\beta\) - endorphin (\(\mu\) & \(\delta\))
- Morphine
- Dynorphin (\(\mu\))

**Notes:**

- **SPINAL CORD:** Dymorphinergic neuron with \(K\) receptors
  - Presynaptic inhibition of both III and IV fibres by enkephalins
  - Pain inhibitory complex: enkephalin (\(\delta\))
CNS

A schematic for an analgesic receptor site may look as shown in the graph on the right with morphine.
Three areas are needed: a flat area to accommodate a flat nonpolar aromatic ring, a cavity to accept another series of rings perpendicular, and an anionic site for polar interaction of the amine group.
Morphine and Codeine:

Morphine exerts a narcotic action manifested by analgesia, drowsiness, changes in mood, and mental clouding. The major medical action of morphine in the CNS is analgesia.
Opiates suppress the "cough center" which is also located in the brainstem, the medulla. Such an action is thought to underlie the use of opiate narcotics as cough suppressants. Codeine appears to be particularly effective in this action and is widely used for this purpose.
Narcotic analgesics cause an addictive physical dependence. If the drug is discontinued, withdrawal symptoms are experienced. Although the reasons for addiction and withdrawal symptoms are not completely known.
Recent experiments have provided some information. A nucleotide known as cyclic adenosine monophosphate (cAMP) is synthesized with the aid of the enzyme adenylate cyclase. Enkephalin and morphine-like drugs inhibit this enzyme and thus decrease the amount of cAMP in the cells.
In order to compensate for the decreased cAMP, the cells synthesize more enzyme in an attempt to produce more cAMP. Since more enzyme has been produced, more morphine is required as an inhibitor to keep the cAMP at a low level.
This cycle repeats itself causing an increase in the tolerance level and increasing the amounts of morphine required.

If morphine is suddenly withheld, withdrawal symptoms are probably caused by a high concentration of cAMP since the synthesizing enzyme, adenylate cyclase, is no longer being inhibited and the victim will experience the toxicities of the increased levels of cAMP.
Heroin:

Heroin is synthesized from morphine by a relatively simple esterification reaction of two alcohol (phenol) groups with acetic anhydride (equivalent to acetic acid). Heroin is much more potent than morphine but without the respiratory depression effect.
A possible reason may be that heroin passes the blood-brain barrier much more rapidly than morphine.

Once in the brain, the heroin is hydrolyzed to morphine which is responsible for its activity.
Synthetic narcotic analgesics may include the followings:

Meperidine (Pethidine®)
Methadone
Noscapine (Antitussive)
Dextromethorphan (Cough suppressant)
Pentazocine
Hydrocodone
Codeine
Hydromorphone
Apomorphine
Narcotic Antagonists:

Narcotic Antagonists prevent or abolish excessive respiratory depression caused by the administration of morphine or related compounds. They act by competing for the same analgesic receptor sites. They are structurally related to morphine with the exception of the group attached to nitrogen.

Nalorphine
Naloxone
Naltrexone
Nalorphine

(N-allyl-normorphine), is an opioid antagonist. It acts at two opioid receptors:
1- At *Mu* receptor it has antagonistic effects.
2- At *Kappa* receptors it exerts agonistic characteristics.

Clinical uses:
Reverse opioid overdose.
Naloxone

Naloxone is an opioid antagonist used to counter the effects of opiate overdose specifically depression of the central nervous system and respiratory system. Used in emergency cases of opioid overdose.
Naltrexone

An opioid receptor antagonist used in the management of alcohol dependence and opioid dependence.
Using naloxone in place of naltrexone can cause acute opioid withdrawal symptoms which lasts for 14 days;

- Sever abdominal cramps
- Diarrhea.
- Nausea.
- Vomiting.
- Agitation.

Using naltrexone in place of naloxone in an overdose can lead to insufficient opioid antagonism and fail to reverse the overdose.
Other opioid alkaloids

Papaverine

Thebaine
Papaverine used for:

-IBS

-Biliary tract spasm

-Ureter spasm

-Cerebral and coronary vasodilator in subarachnoid hemorrhage and coronary artery bypass surgery.

-Papaverine may also be used as a smooth muscle relaxant in microsurgical procedures.
-Used in the treatment of erectile dysfunction injected in penile tissue causing direct smooth muscle relaxation and consequent filling of the corpus cavernosum with blood resulting in erection.
Mechanism of Action:
Through inhibition of phosphodiesterase causing elevation of cAMP levels.

Toxicities:
Ventricular tachycardia
Synthetic analogues...

Methadone

Meperidine (Pethidine®)
Pentazocine
Lecture review...

Any questions?
Thank You