Substance Abuse
PHG 414

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Welcome Back Dears
Central Nervous System Depressant
You should be able to know:

- **Identify the different classes of CNS Depressant**
- **Determine pharmacological actions of CNS Depressant**.
- **What is Alcohol abuse, effect and treatment**
- **Opioid abuse, types, effect, analysis and treatment**
CNS Depressant
CNS Depressant
Natural CNS Depressant

Opiate raw materials and opioid

Illicit production:

Opium is a complex mix of an alkaloid fraction (10-20%) together with sugars, protein, lipids and other gummy substances. The alkaloid fraction consists of about 40 alkaloids with 5 major ones belonging to two major and important groups of alkaloids. The first is phenanthrene group including morphine, codeine and thebaine. The second one is isoquinoline group including papaverine and noscapine (narcotine).

Illicit opium products types:
1-Raw opium
2-Medicinal opium
3-Prepared opium
4-Opium dross
Opiate raw materials and opioid

Illicit production

1-Raw opium

*Indian opium*, obtained by incision of the unripe poppy capsules.
*When fresh it is sticky, has atar-like consistency, a medium brown color*, and easily molded into different shapes and forms depending on the method of packing and country of origin.
*As raw opium ages, it with gradually become hard and brittle, and the color become darker, especially at the surface.*
*It is readily dissolve in water* yielding a brown colored solution with liquorices-like odor and leaving vegetable debris of poppy capsule and leaves.
*Bannan pulp, rosin, powdered poppy, capsules gum, etc.. are commonly used as adulterants.*
*Raw opium can be distinguished by its characteristic odor the presence of plant fragments and the presence of meconic acid and porphyroxine.*
Opiate raw materials and opioid

Illicit production

2-Medicinal opium

is generally one of the three preparations

1-Granulated or powdered opium: (depending on the final mesh size of the product), and is an opium which dried at 70°C and whose morphine content is adjusted to pharmacopeia requirements of 10-15% w/w, by the addition of lactose, powdered coca husk or rice starch.

2) Deodorized opium or de-narcotized opium: this material is prepared by treating opium with petroleum ether, which removes both narcotine (noscapine) and the characteristic odor of opium. Morphine concentration also 10-15% w/w.

3) Concentrated opium= Pantopon= Omnopor= papaveretum: it is a mixture of morphine, codeine, papaverine and noscapine as HCl salts with the morphine content adjusted to 50% w/w.
Opiate raw materials and opioid

Illicit production

3-Prepared opium

It is an opium extract suitable for smoking.

It is produced by boiling raw opium in water after filtration to remove insoluble materials evaporating them till roasted.

The roasted product is re-extracted with water and evaporated to a black residue known, in south East Asia as chandoo or chandu that means opium extract for smoking.

It contains about 8% morphine.

Prepared opium, like raw opium give positive color test for meconic acid but differ from raw opium in the absence or near absence of plant fragments.

The characteristic odor of raw opium is absent and gives no positive test for porphyroxine.
Opium raw materials and opioid

Illicit production

4-Opium dross

is the residue that remains in the opium smoking pipe after the opium dross, raw opium and prepared opium have been reported in south East Asia. Dross is both eaten and re-smoked after being added to prepared opium. Dross does not give a positive color test for either meconic acid or porphyroxine.

Opium constituents of forensic significance

Morphine, codeine, thebaine, papverine, noscapine and meconic acid are the six major while porphyroxine the minor one.

Opium Constituents of Forensic Significance

- Morphine
- Codeine
- Thebaine: 6-methoxy codeine
- Pappaverine (Narcotine)
- Papaverine
- Noscapine
Opiate raw materials and opioid

1) Crude Morphine

The crude morphine obtained on the illicit market could be very high or very low a quality depending on the preparation and purification procedures. For preparing morphine there are three methods as following:

Method I (lime water method): 1 kg opium+200 gm lime (calcium hydroxide)+2 L H₂O, this step allows the complete extraction of morphine, codeine and partial extraction of thebaine, while noscapine not extracted add to the mixture 250 gm NH₄Cl, 500 ml ethanol and 500 ml diethyl ether then shake and allow to separate. This step allows the removal of codeine, thebaine and minor alkaloids in the ethereal layer and precipitate of morphine in the aqueous phase in the form of light brown crude morphine base then filter and purify and decolorize by boiling under reflux for 30 minutes with 2L H₂SO₄ and 250 gm charcoal after that filter using NH₄OH prepared morphine base after drying will get white morphine.
Method II:

Opium + H2O or Diluted HCl → pH+6.5 → ppt of papaverine and noscapine

Adjust pH at 9 with NH4OH

White powder of very pure morphine base as white powder

Filter

To remove thebaine and codeine

Ppt of Morphine wash with benzene, Et2O or EtOAc

Method III:

Opium with water or diluted acid (adjust the pH to 9.0) it will give a precipitate of a relatively impure or brown mixture is precipitated consisting mainly of morphine and noscapine in the ratio of 2:1 or 1:2. This method is typical in south west Asia crude morphine.

Crude morphine usually contains codeine and noscapine as impurities and is used for preparation of heroin pure morphine can be obtained by crystallization in the form of SO4, tartarate or HCl salts
Opiate raw materials and opioid

2) heroin

Heroin (also known as diamorphine, diacetylmorphine):
- is a semisynthetic analog of morphine. It is more water soluble, more rapidly absorbed and 2-3 times more potent as analgesic than morphine. Heroin is rapidly deacetylated in the body and in alkaline media to morphine. It belongs to the internationally controlled narcotic analgesic with morphine, codeine and some other synthetic drugs.

Illicit production:

the illicit production of heroin begins with crude morphine. It is a simple one step acetylation reaction, as the following:

• Preparation of crude morphine from raw opium as before.
• Acetylation of crude morphine with Ac₂O under reflux for 2h.
• Precipitation of crude heroin base by neutralization of the acidic mixture with Na₂CO₃ filtered and washes the ppt with water.
• Purification of the crude heroin base by dissolving in boiling water containing citric acid and charcoal the filter and use Na₂CO₃ to precipitate then filter and dry.
• Heroin HCl salt is prepared if required by addition of the required quantity of HCl to acetone solution of the purified heroin base.
Adulteration of Heroin:
Diluents or additives, such as carbohydrates (lactose, sucrose, and starch), alkaloids (caffeine, quinine, strychnine, yohimbine), local anesthetics (procaine), and barbiturates (barnitone) as well as other were detected in illicit heroin samples.

In Egypt, samples of illicit heroin seizures were totally substituted with a mixture of the highly toxic alkaloids. Strychnine and yohimbine that are commonly used in some pharmaceutical preparations to increase the general fitness, and to induce aphrodisiac activity.

• In another sample heroin was also totally substituted with baby milks to which grounded “Enterovioform” tablets were add to produce beige or light brown product.

NB: Poorly manufactured heroin is characterized by the presence of 5% or more of 6-monoacetyl morphine and morphine. Such hydrolytic products are formed primarily due to the use of excess HCl during the manufacturing process of heroin HCl.
Illicit product and source determination:

*Each major geographic source area produces a heroin that on average is different from those found in the other producing area as a result each major source area produces a heroin that can usually be recognized as a chemically distinct type.

*It is of interest to note that the marked variation in heroin content and contaminants could indicate the production source and the possible trafficking route.

*Four areas of the world which are generally recognized as being major sources of opium and heroin. South East Asia. South West Asia especially Afghanistan. Mexican production especially in Guatemala. South America especially. northeastern Peru and Colombia.

**Heroin:** is most frequently encountered as either the free base or as the HCl salt. Heroin also sometimes present as tartarate and even less frequently as citrate. On even more occasions, a heroin sample will be some combination of HCl, tartarate and citrate salts, along with small quantity of heroin base.
Opiate raw materials and opioid

2) Heroin

• Major constituents in Heroin Samples:

Except of rare occasions, a heroin sample will contain some detectable quantity of both 3- and 6- acetylmorphine and acetyl codeine. The presence of 3. A.M. in a heroin sample is generally attributed to incomplete acetylation of morphine, while the presence of 6. A.M. is generally attributed to hydrolysis of heroin.

*All other opium related alkaloidal impurities found in a heroin sample are due to their presence in the morphine prior to acetylation since papaverine does not contain a labile hydrogen and is quite stable, it remains unchanged by acetylation process.

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Opiate raw materials and opioid

CNS Depressant

Natural CNS Depressant

2) Heroin

**Major constituents in Heroin Samples:**

However, noscapine is not stable to vigorous acetylation conditions, and if these conditions are prolonged, major quantities of the no

Occasionally codeine is detected in heroin sample, while acetylcateine is virtually always present at significant levels. In fact, like 6-acetyl morphine, acetyl codeine can be present at levels greater than 50% relative to heroin. In these cases, the analyst should be aware that the absence of papaverine and noscapine could indicate that the heroin was prepared from morphine that was obtained via a codeine de-methylation procedure.
Administration:
• Opium is commonly administered by oral route particularly in the Middle East region, prepared opium by inhalation through smoking, and morphine HCl, SO4 or tartarate by oral, subcutaneous, IV or IM.
• Heroin is commonly administered by inhalation through smoking (usually heroin base) and snorting or snitting (usually diluted heroin HCl. High quality heroin HCl is usually abused through subcutaneous (Jaypopping) and intravenous injection (mainlining). Heroin HCl, when taken by parenteral route, the powder is first dissolved in H2O through gentle heating.

Pharmacological Effects:
• Opium and opiates are CNS depressants. They produce general narcosis, analgesia, sedation, euphoria, constipation, respiratory depression due to decreased medullary sensitivity to CO2, cough depression, nausea, vomiting, hypotension and miosis (pin-point pupil). These effects indicate narcotic intoxication and addiction.
• Heroin like morphine is a CNS depressant. It is 2-3 times more potent as analgesic than morphine but less safe on respiratory center. It resembles morphine in control of diarrhea but fewer tendencies to produce constipation. It is more lipids soluble and then readily penetrates the BBB (Blood Brain Barrier). It is rapidly converted into the body to MAM (Mono Acetyl Morphine) and then to morphine.
Opiate raw materials and opioid

**Dependence:**
opium and opiates are narcotic analgesic. They produce rapid and severe psychic and physical dependence.

**Heroin** intoxication produces like morphine, general narcosis, analgesia and sedation but it is characterized by greater Euphoria.

**Abstinence syndrome:**
*Opium and opiates are specifically bound to the opiate receptors in the cell membrane of neuron and smooth muscle cells.
*The organism develops a need for continuous intake of the drug otherwise a physiological disturbance develops known as withdrawal or abstinence syndrome due to autonomic hyperactivity.
*The sympathetic effects are manifested by lacrimation, salivation, sweating, piloerection, dilatation of the pupil, increase blood pressure, and increase heart rate, while the parasympathetic effects include, nausea, vomiting, abdominal pain, diarrhea, anxiety, tremors and convulsion.
*In heroin, it appears after 12-14 hours of abstinence and is characterized by light perception, lacrimation, and insomnia, dilatation of the pupil and twitching of various muscle groups.
*The symptoms reach peak intensity 48 hours after the last dose and remain intense until 72 hours of abstinence then begin to decline.

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**CNS Depressant**

**Natural CNS Depressant**

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms of Opioid Withdrawal</th>
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<td><strong>Symptoms</strong></td>
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<tr>
<td>Anorexia &amp; nausea</td>
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<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Hot &amp; cold flushes</td>
</tr>
<tr>
<td>Bone, joint &amp; muscle pain</td>
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<tr>
<td>Insomnia &amp; disturbed sleep</td>
</tr>
<tr>
<td>Cramps</td>
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<tr>
<td>Intense craving</td>
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</table>

### Opiate Withdrawal Timeline

- **Symptoms Begin**
- **Last Dose**
- **Symptoms Peak**
- **Diarrhoea**
- **Opiate Withdrawal Timeline**
- **Post-Acute**
- **Withdrawal Syndrome**
- **Heroin Withdrawal Timeline**
- **Peak**
- **Subside**
- **Start**
- **6-12 Hours**
- **1 Week**
- **1-3 Days**
- **30 hours**
- **72 hours**
- **Symptoms Persist for weeks, months, or even years**
- **Drug Cravings**
- **Nausea**
- **Vomiting**
- **Stomach Cramps**
- **Diarhoea**
- **Goosebumps**
- **Depression**
Forensic analysis of opium, crude morphine and heroin

*It is difficult to distinguish between a positive color test for morphine and one for heroin.
*Additionally chromatography systems that are suitable for the analysis of opium/morphine samples need only to be modified slightly to also be suitable for the analysis of heroin samples.
*Finally, it is clear that the techniques utilized for acquisition of spectral data for heroin and morphine differs only in minor detail

Properties of opium illicit products:

• **Raw Opium** may be distinguished from other opium preparations by the presence of plant debris, meconic acid, and the trace alkaloid porphroxine.
• **Prepared Opium** will contain meconic acid, some quantity of dross, no plant fragments or porphyroxine.
• **Crude morphine:** can be distinguished from prepared opium by the absence of plant fragments, porphyroxine, meconic acid, and usually the absence of characteristic odor of opium.
Opiate raw materials and opioid

Forensic analysis of opium, crude morphine and heroin

1-Color tests:
Color tests are highly sensitive it needs only less than 1 mg. several different reagents are typically employed for color and anion testing of opiates.

• Marquis Test:
Reagent 1: 8-10 drops of HCHO 37%. Add to 10 ml of glacial acetic acid. Reagent 2: Concentrated H₂SO₄

METHOD:
• For opium: place a small amount of opium on spot plate add 3 drops of water and smear the sample against spot plate with glass rod spatula. Transfer a drop of the first quell to another depression of spot plate, add 1 drop, HCHO and 3 drop H₂SO₄.
• For Morphine, codeine and heroin, place small amount of the suspected material on spot plate add 1 drop of HCHO and 3 drops of H₂SO₄

Result: violet to reddish purple color indicates the possible presence of opium or morphine or codeine or heroin.
Opiate raw materials and opioid

Forensic analysis of opium, crude morphine and heroin

2-Ferric Chloride Test: (meconic acid test)
5% aquous solution of FeCl₃, same procedure like above for opium give brownish purple color indicates the possible presence of opium.

3-Hydrochloric acid Test (porphyroxine test): place small amount of opium on spot plate, add 1 drp of HCl and heat gently give red color indicates the possible presence of opium.

4-Associated anion tests:
From a forensic point of view, anion testing is applicable to all opiate samples with, of course, the exception of dross and raw or prepared opium. Morphine is commonly encountered as the HCl salt, the SO₄ salt, or as free base while on occasion it may be present as the tartarate salt.
Opiate raw materials and opioid

Forensic analysis of Opiates

Chromatographic Analysis:

• **TLC:** silica gel: Standard: heroin, morphine, codeine, acetyl codeine, 6 MAM, papverine and noscapine. **Visualization:** UV, Dragendorff’s reagent, acidified sodium iodoplatinate give blue purple spot with opium alkaloids.

• **GLC:** Carrier gas N2. interval standard DoCoSa or n-alkane. Derivatization N,O-bis trimethylsilylacetamide (BSA). Standard solution for heroin, 6AM and acetyl codeine.

• **HPLC:** For opium and morphine: Rp-18, Detector UV at 280 nm. **Mobile phase:** water-CH₃CH- trimethylamine (40:60:0.1) HPLC is probably the method of choice for the quantification of opium and morphine samples. **For heroin,** related alkaloids and adulterants: Detector UV diode array, monitor three wave lengths: 210, 228 and 240 nm Colum ODS. **Mobile phase:** water-CH₃CN-GLACIAL ACETIC ACID (89:10:1)

Spectroscopic Analysis: IR, MS, GC-MS:
Detection and assay of opium and opiates in biological samples. All Opiates in the urine does not indicate which opiates were used.
Opiate raw materials and opioid

Metabolic and Excretion of Opiates

• Heroin is rapidly deacetylated within 3-20 minutes to O\textsuperscript{6} – monoacetylmorphine, when is then further hydrolyzed to morphine at a lower rate (2-3h). The major metabolites of heroin, found in urine (20-40h) after IV administration, are morphine 3-O-glucuronide (38.2%), free morphine (4%), O6-MAM (1.3%) and unchanged heroin (0.1%).

• Morphine major metabolites found in urine 20-48 hours after parenteral administration, are free morphine (10%), conjugated morphine as 3-O-glucuronoids (major), 6-O-glucuronoid and 3,6-O-glucuronoid (60-70%)

• Codeine major metabolites, found in urine 24 hours after oral administration are free or conjugated codeine (40-70%) and free or conjugated morphine (5-15%).