THE NORTHERN HOSPITAL

MORPHINE

"Nymphs Listening to the Songs of Orpheus", oil on canvas, 1853 Charles François Jalabert
The Walters Art Museum, Baltimore, Maryland.

"...As he sang these words to the music of his lyre, the bloodless shades were in tears. Tantalus made no effort to reach the waters that ever shrank away. Ixion's wheel stood still in wonder, the vultures ceased to gnaw at Titus' liver , the daughters of Danaus rested from their pitchers and Sisyphus sat idle on his rock. They say, for the first time, the faces of the Furies were wet with tears, won over by his song: the king of the deep, and his royal bride, could not bear to refuse his prayer, and called for Eurydice..."

Ovid, The Metamorphoses X 40-45, 8 A.D

Orpheus was a demigod, or perhaps even a god, no one was quite sure. He lived amoung mortals in the time of Jason, long long ago. His mother was the Muse Calliope. Some said that his father was Oeargrus, King of Thrace, but others whispered, that his father was in fact the great god Apollo. Only one thing was sure, his ability to play the lye far surpassed any mortal hand, in this ability there was no doubt, he was surely a god. His music was so divine, that any mortal who heard it, immediately stopped what they were doing, instantly entranced, the outside world for them ceased to exist while he played. But more than this, Orpheus' music captivated nature itself. Animals including great and ferocious beasts were quieted. The trees and rivers, the forces of nature, the wind and the rain were calmed. Even inanimate nature, the rocks and the Earth were soothed. It was not long before the Maenads, who were the devoted and fanatical followers of the great god of wine, Dionysus, heard stories of Orpheus and his lyre. Renowned for their tranced frenetic orgiastic gyrations at the celebrations of Bacchus, they became curious when told that Orpheus' music surpassed even that of the great Bacchanal feasts. They sought out Orpheus in the deepest forest, and found him, spying on him hoping to hear him play. Eventually they were rewarded and instantly they became his devoted followers, spending most of the time now with Orpheus and not Dionysus.

Orpheus' fame eventually reached the ears of the hero Jason, who was about to embark on his great quest for the Golden Fleece. Jason knew that his mission would be long and perilous, and his crew of Argonauts, volatile demigods to a man, would be difficult to control. He determined to recruit Orpheus to his cause. Orpheus agreed, eager to join a great adventure. Many times over he would save Jason's mission from internal discord and disaster. When disputes broke out on the Argo as it sped over the deep seas, Orpheus would simply start playing his lyre. Very soon, the seething crew would be distracted from their agitations and all would instantly calm and in unison listen spellbound each lost in their deepest innermost thoughts. By his hypnotic music he was even able to distract the Argonauts from the notorious Sirens, whose sweet songs would lure men in their ships to their deaths on the jagged rocks. Only the great Odysseus had ever heard their voices and survived.

After the successful voyage of the Argonauts, Orpheus, weary of constant danger and hardship, returned to his native Thrace. Having been long devoid of female companionship, he very soon fell passionately and hopelessly in love with the river nymph Eurydice. She, enchanted by his music, reciprocated his feelings and they quickly made plans to marry. But tragedy struck on the wedding day. Eurydice was bitten on the heel by a deadly serpent, and she quickly died in agony. Inconsolable Orpheus persuaded the gods to allow him to descend to the underworld to plead with Hades himself to give him back Eurydice. As Orpheus was a demigod, this was allowed, a privilege no mere mortal would have been given, but the gods warned Orpheus that Hades had never let anyone, apart from Persephone, leave the underworld and so his chances of success were very slim indeed. Undeterred, Orpheus descended the underworld where he begged on his knees to Hades and his Queen Persephone to release Eurydice. But Hades was

unmoved. Unmoved until Orpheus began to play his lyre and softly tell of his love of Eurydice. The underworld had never heard such sweet and haunting tones. The poet Ovid later wrote of the astonishing reaction of all those in the underworld who heard Orpheus that day....

"...As he sang these words to the music of his lyre, the bloodless shades were in tears. Tantalus made no effort to reach the waters that ever shrank away. Ixion's wheel stood still in wonder, the vultures ceased to gnaw at Titus' liver, the daughters of Danaus rested from their pitchers and Sisyphus sat idle on his rock. They say, for the first time, the faces of the Furies were wet with tears, won over by his song: the king of the deep, and his royal bride, could not bear to refuse his prayer, and called for Eurydice..."

Both Hades and Persephone had never been so emotionally affected. Hades, against all his instincts, granted the release of Eurydice, but on two conditions. Firstly Orpheus must leave the underworld, as if alone, so as not to alert the other shades that he had allowed someone to return to the world of the living. Eurydice could follow discretely behind him, and would not be detained by Charon the Ferryman of souls, and secondly, under no circumstances, was Orpheus to look back toward Eurydice. As Orpheus was leaving however, began to fear that Eurydice was not able to keep up on account of her limp from the deadly snake bite, or that perhaps Hades had changed his mind and detained her. No longer able to stand the strain, he glanced back over his shoulder, only to see Eurydice immediately fall back into the thin mist of the underworld. Orpheus tried to re-enter the underworld but Charon barred his way. No begging or pleading could persuade Charon to let him back across the river Styx, and not even his lyre could change his mind. Orpheus spent seven days on the banks of the Styx in inconsolable grief, until he finally realized that Eurydice would never be returned to him. He sadly and slowly made his way back home. Once back in Thrace he resolved never to have anything more to do with women, and men now became his preferred option. But this infuriated the Maenads. They grew so angry, they became entranced as they would for a great feast, and in this state when aroused their fury could be terrible to behold. They went to Orpheus, and asked him to play for them, but he refused, where upon they fell upon him in a frenzy, shrieking so loudly that even when he did begin to play they did not hear him. They torn him apart limb by limb. They placed his head on his lyre and threw it into the sea. Eventually the head and lyre reached the island of Lesbos. It was said that the lyre still played softly and that the head kept whispering Eurydice's name. The gods of Olympus, who had witnessed all that had happened, took pity on Orpheus. They took his Lyre and placed it amoung the Constellations of the firmament. They then took Orpheus' soul and reunited it with that of Eurydice forever in the Elysian Fields, the paradisiacal realm of the kingdom of the dead.

Later on one of the gods of Olympus, greatly saddened at the death of Orpheus, bequeathed to humanity a certain nectar, so ancient its origins derived from before recorded history. This nectar was to replace the soothing music of Orpheus, by which mortals could gain peace from pain and despair, just as the notes of Orpheus's lyre had once soothed distracted souls. Some said this god was Apollo, others that it was Artemis, but yet others whispered that on the basis of a close study of etymology, this god was in fact the true father of Orpheus - a very ancient god - even older than the twelve Olympians. His name was Morpheus, the god of dreams. He gave the gift of dreamlike music to his son to give to humanity, but when his son was killed, he gave humanity a god-like nectar to replace Orpheus' music. Even today we still possess this nectar of the gods - we call it morphine, after Morpheus himself, the true father of Orpheus.

MORPHINE

Introduction

Morphine is the prototype opioid analgesic.

It is obtained from the opium poppy plant and has been known and used since before recorded history.

Opioid analgesics are used for the treatment of moderate to severe pain, diminishing both the sensation and the affective response to pain

They block *all forms* of pain, not just pain arising from tissue damage and inflammatory processes. [1]

The normal clinical doses used also dampen the patient's emotional response to the pain, perhaps more effectively than blocking the pain (i.e. pain may still be noted by patients but they can tolerate it or cope with it better). [1]

The main toxic effects of morphine are CNS and respiratory depression, which may be lethal.

Morphine is a pure opiate agonist

Its specific antidote is naloxone.

Morphine is generally the *preferred opioid analgesic* for moderate to severe pain because of long term familiarity, availability and cost (rather than any superior efficacy).

Other opioids may be used where adverse effects of morphine are unacceptable or there a specific contra-indication such as allergy, or there is concern about the effect of active metabolites. [3]

See also separate Documents on:

- **Opioid Overdose, (Toxicology Folder)**
- **Heroin Overdose, (Toxicology Folder)**
- **Opioid Toxidrome**
- **Opiate Withdrawal, (Toxicology Folder)**
- **Naloxone, (Drugs Folder)**

History

The analgesic and sedating effects of opium have been know since before recorded history.

By the mid 1960s, it was found that opiate drugs exerted their actions via specific naturally occurring endogenous receptor sites in the body.

The German pharmacist **Friedrich Serturner** (1783-1841) discovered the major active component of opium in 1805, which he named morphine after the Greek god Morpheus, the god of dreams.

Chemistry

Morphine, is the principal active **alkaloid** of the plant *Papaver somniferum*, (the **Opium poppy).**

Right: Flowers of Papaver somniferum, (the Opium Poppy) Middle: Capsule of the Papaver somniferum plant. Right: latex (opium) exuding from an incised poppy capsule.

Classification

Opioids may be classified according to:

1. Derivation
2. Receptor activity

Opioid Derivation Classification:

1. **Natural Alkaloids of Opium:**
    - Benzylisoquinolines:
        - ♥ Papaverine
        - ♥ Noscapine
    - Phenanthrenes:

- ♥ **Morphine**
- ♥ Codeine
- ♥ Thebaine

2. **Semi-synthetic Derivatives:**
   - Diacetylmorphine (heroin)
   - Hydromorphone
   - Oxymorphone
   - Hydrocodone
   - Oxycodone
3. **Fully Synthetic Derivatives:**
   - Morphinans:
     - ♥ Levorphanol
   - Benzmorphans:
     - ♥ Pentazocine
     - ♥ Phenazocine
     - ♥ Cyclazocine
   - Propionanilides:
     - ♥ Methadone
   - Phenylpiperidines:
     - ♥ Pethidine
     - ♥ Fentanyl
     - ♥ Remifentanil
     - ♥ Alfentanil
     - ♥ Sufentanil
     - ♥ Carfentanyl

Opioid Receptor Activity Classification:

1. **Pure agonists**:

   These are pure agonists of specific opioid receptors (notably the mu receptor)

   There is no limiting ceiling effect with the *pure* agonists,

   Examples include:

   - Morphine
   - Fentanyl
   - Pethidine

2. **Mixed agonist - antagonists**:

   These have opposing effects at distinct receptor subtypes, i.e agonist activity at one receptor type and antagonist activity at another receptor type

   Examples include:

   - Nalorphine
   - Pentazocine

3. **Partial mu agonists**:

   These agents produce a less than maximal response and, therefore, have a lower *intrinsic* activity.

   The partial agonist (and mixed agonist - antagonist) opioids, demonstrate a ceiling response above which an increase in dose does not produce any additional increase in effect.

   Partial agonists are able to **antagonize** the effects of large doses of **full** agonists

   Examples include:

   - Buprenorphine

A fourth group can be described as **pure antagonists**, of which **naloxone** is an example.

Physiology

Opioid receptors are distributed widely in the:

1. Brain
2. Spinal cord
3. Digestive tract.

The three principle opioid receptors are:

Receptor	**Opioid class**	**Location**	**Possible Functions**
Mu Subtypes include: μ_1, μ_2, μ_3	**Endorphins**	Brain: The highest concentration is found in the limbic system. Spinal cord Peripheral sensory neurons GIT	Analgesia/ physical dependence Respiratory depression/ miosis/ Euphoria/ reduced GIT motility/ physical dependence Possible vasodilation
Kappa Subtypes include: κ_1, κ_2, κ_3	**Dynorphins**	Brain: Spinal cord Peripheral sensory neurons	Analgesia/ convulsant effects/ dysphoria/respiratory depression/ reduced GIT motility
Delta Subtypes include: δ_1, δ_2	**Enkephalins**	Brain: Peripheral sensory neurons	Analgesia, (less than mu)

The endogenous opioids include:

- Dynorphins
- Enkephalins
- Endorphins
- Endomorphins
- Nociceptin.

Preparations

Morphine as:

Tablets:

There are a vast number of formulations available:

- There are many **immediate release** preparations available.
- There are many **controlled release** (12 - 24 hour) tablet preparations available (e.g. MS Contin).
    - ♥ These must be swallowed whole; and not crushed or chewed.
    - ♥ Doses generally range from **5 - 120 mg.**

Liquid formulations:

There are many available preparations and strengths, including:

- 1 mg/ml
- 2 mg/ml
- 5 mg/ml
- 10 mg/ml

Ampoules:

Morphine sulphate:

- **10mg/1ml ampoules**
- **30mg/1ml ampoules**

Mechanism of Action

Opioids interact with one or more subtypes of opioid receptors (e.g. mu, kappa, delta) at supraspinal, spinal and peripheral sites to produce analgesia and a multitude of other effects.

Opioid mimic the effects of the endogenous opioids by activating opioid receptors in the central nervous system, peripheral nervous systems

Current potent opioid analgesics are mu agonists, although specific delta and kappa agonists may also produce analgesia.

Opioids act by: [1]

- Presynaptic inhibition of neurotransmitter release from C-fiber terminals.
- Postsynaptic inhibition of evoked activity in nociceptive pathways.
- Disinhibition of other circuits regulating nociceptive transmission.
- Supraspinal opioids increase descending inhibition of spinal nociceptive transmission

Morphine is **most active at the mu receptors**, but also has some activity the kappa and delta receptors.

Pharmacodynamics

Therapeutic effects include:

1. Analgesia
2. Sedation
3. Anxiolysis
4. Cough suppression:
    - Via a direct effect within the medulla of the brain stem.

Pharmacokinetics

Absorption:

Morphine can be given orally, IV, IM, SC and intathecally

Oral:

3 mg of oral morphine ≈ 1mg IV morphine

Do not crush controlled release products as this will result in more rapid and unpredictable absorption

Peak analgesia occurs within 60 minutes after **conventional oral liquid** preparations. [3]

IM & SC:

Absorption of morphine sulfate after **intramuscular** and **subcutaneous** injection is fairly rapid.

Peak effects are generally as follows:

- Peak analgesia occurs 30 to 60 minutes after **IM** injection. [2]

- Peak analgesia occurs 50 to 90 minutes after **SC** injection. [2]

IV:

Peak analgesia occurs within 20 minutes after **IV** administration. [2]

Epidural and Intrathecal (Spinal) Morphine:

Epidural and Intrathecal (or spinal) morphine can provide significant safe analgesia for 12 - 24 hours

Distribution

- Morphine is distributed widely throughout the body
- Morphine diffuses across the placenta
- Trace amounts are found in breast milk.
- It is about 35% is protein bound, mainly to albumin.
- In older patients, the volume of distribution is considerably reduced and initial concentrations of morphine are therefore correspondingly higher.

Metabolism and excretion:

- Morphine is metabolized principally in the liver by conjugation with glucuronic acid.

  The principal metabolites are morphine-3-glucuronide and morphine-6-glucuronide.

  Morphine-6-glucuronide is pharmacologically active and has a half-life somewhat longer than morphine.

- Elimination half-life from serum is approximately 1.5 - 2 hours in healthy subjects and 90% of the dose is recovered in urine within 24 hours.

  Approximately 7 - 10% of the dose is recovered in faeces, the majority after conjugation and excretion via bile.

Indications

Indications in the ED include:

1. Moderate to severe acute pain
2. Anxiolysis:
   - Including cases of acute pulmonary edema

3. Adjunctive sedation in intubated patients

4. Palliation for end of life care

Indications outside of the ED include:

5. Moderate to severe chronic pain:

    - Including for palliative care

6. Opioid adjunct during general anaesthesia

7. An option in anesthetic pre-medication

Contra-indications/precautions

1. Respiratory:

    Use with caution in patients at risk of respiratory depression:

    The following are relative contraindications:

    - Severe obstructive airways disease
    - Those at risk of upper airways obstruction
    - Obstructive sleep apnea

2. CNS:

    - Patients with a depressed conscious state.

3. CVS:

    - Hypotensive patients, (relative); titrate with caution.

4. Renal impairment, (relative contraindication):

    - Morphine and its active metabolites accumulate in renal impairment and have a longer half-lives which may result in respiratory depression and delirium.
    - In these patients, analgesia may last for 6, 8 or even up to 24 hours following a standard dose.

5. Hepatic impairment:

    - Use with *caution* in severe hepatic impairment (relative contraindication) - may cause excessive sedation or coma.

6. Concomitant use with other central nervous system depressants, effects are synergistic

7. Elderly:

   - Opioid dose requirement decreases progressively with age.
   - There is an increased risk of adverse effects including cognitive impairment, sedation, respiratory depression and falls.
   - Use lower initial doses and titrate cautiously to effect.

8. Neonates and infants:

   - Neonates and infants up to approximately 12 months are more susceptible to respiratory depression associated with opioid use. Start with a low dose and titrate to effect.

9. Known hypersensitivity to morphine.

Pregnancy:

Morphine is classified as a **category C** Drug with respect to pregnancy.

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations.

These effects may be reversible. Specialised texts should be consulted for further details. [1]

Long-term use of morphine during pregnancy may result in a neonatal opioid withdrawal state. Babies born to mothers who are physically dependent on morphine may also be born physically dependent on it.

Breast feeding:

Morphine is excreted in human milk

It is compatible in usual analgesic doses used in the perinatal period; caution with high-dose extended-release preparations, as there are no data. [1]

It is safe to use *occasional* doses of opioids but avoid codeine. [3]

Use repeated doses only with caution, especially if infant is premature or < 4 weeks old; monitor infant for sedation and other adverse effects. [3]

In general breastfeeding is generally not recommended while a patient is receiving morphine.

Withdrawal symptoms have been observed in breastfed infants when maternal administration of morphine sulfate is stopped. [2]

Adverse Effects

Adverse effects include:

1. CNS:
    - Depressed conscious state, with attendant risk of airway compromise.

      This is a principle cause of death in overdose/ toxicity.
    - Euphoria/ dysphoria/ delirium/ hallucinations
    - Occasionally there can be a lowering of seizure threshold, especially in those with convulsive disorders.
2. Respiratory depression/ arrest:
    - **This is a principle cause of death in overdose/ toxicity.**
    - **The risk is dose related and synergistic with other CNS depressants, including alcohol**
3. GIT:
    - Nausea and vomiting:
        - ♥ Nausea and vomiting is thought to occur via direct stimulation of the chemoreceptor trigger zone (CTZ).
        - ♥ It is a very common reaction.
        - ♥ An antiemetic may be given prophylactically
    - Decreased GIT motility
        - ♥ Delay in gastric emptying
        - ♥ Constipation, this is common with **prolonged** use.
4. CVS:
    - Hypotension:
        - ♥ Usually with larger doses, IV and rapid administration
        - ♥ Orthostatic hypotension in ambulatory patients.

- Bradycardia:
    - ♥ Usually with larger doses, IV and rapid administration

5. Allergic reactions:
    - Minor local histamine release is common and benign.
    - Histamine induced hypotension - usually mild
    - True IgE mediated anaphylaxis is **very rare**
6. Urinary retention:
    - This may occasionally occur due to increased bladder sphincter tone.
7. Dependence/ addiction:

    Addiction is a compulsive use to the detriment of physical and/or psychological and/or social function.

    It can be physical and/or psychological:

    Physical dependence:

    - **This is common.**
    - **Withdrawal symptoms** can occur if *chronic* treatment is stopped suddenly or an antagonist is given.

    See also separate Document on Opiate Withdrawal Syndrome, (Toxicology Folder).

    Psychological dependence:

    - This is more common in those with a general history of substance abuse.

    See also separate Document on Opiate Withdrawal

8. Tolerance:
    - Tolerance (increasing dosage to achieve the same effect) may develop upon repeated administration of morphine.
    - Tolerance can develop rapidly, particularly in intravenous drug users who use morphine in the absence of pain.

Dosing

Individual dosing can vary widely depending on the exact indication, whether the pain is acute or chronic pain and the degree of habituation to opioid that the patient may have.

For acute moderate to severe pain:

Adults IV:

For acute moderate to severe pain situations in the ED doses are usually titrated IV according to response / sedation scores.

In general terms, give: [5]

- **2.5 to 5mg IV** as an initial dose, then titrated to effect every 5 to 10 minutes with further incremental doses of 2.5 to 5mg IV.

- In elderly patients or those with cardiorespiratory compromise, an initial morphine dose of less than 2.5mg IV and incremental doses of 0.5 to 1mg should be considered.

- If morphine is contraindicated, consider **fentanyl** at 25 to 50 micrograms IV as initial equivalent dose.

There is no strict upper limit of dosing, but generally once doses of around **30 - 40 mg** have been reached, the risks of excessive sedation will begin to outweigh those of possible benefit, and other drugs/ strategies will need to be considered.

Opioid antagonists and facilities for administration of oxygen and control of respiration should be available during and immediately following any parenteral administration.

Anti-emetic is given either prophylacticlly or as required:

Options include:

- Metoclopramide 10 mg IV

- Prochlorperazine 12.5 mg IV

- Granisetron 1 mg IV

- Ondansetron 4 mg IV

Children IV Dosing:

- **0.05- 0.1 mg/kg**

  To a maximum of 5 mg by slow incremental injection over 5 minutes or longer

IM/ SC Dosing

Dosing requirements can vary considerably from patient to patient, according to:

- Degree of distress
- Age
- Co-morbidities
- Other medications
- Previous habituation
- The sedation score

Adults IM:

In *general terms*, the standard dosing range is:

- **2.5 - 20 mg IM or SC every 4 hours - 6 hours.**
- Oral *immediate release* dosing: **10-30 mg/dose 4 hourly**
- Oral *slow release* dosing: **30-60 mg/dose 12 hourly**. Some preparations may be dosed 24 hourly.

Children IM:

Morphine sulfate is given by IM or SC injection in doses of:

- **0.1 to 0.2 mg/kg bodyweight to a maximum of 15 mg.**

Injection may be repeated every four to six hours.

Infusions:

Adults:

- Standard IV infusion dosing is around **1 -5 mg / hour.**

Children:

- IV infusion, initially 0.02 - 0.04 mg/kg/hour [3]

  To a maximum dose of 4 mg/hour is recommended. [2]

Acute pulmonary edema:

Doses should be **conservative**, (**1 - 2.5 mg IV**) and carefully titrated to effect, to around **5 mg if required.**

The benefits of anxiolysis have to be carefully weighed against those of excessive sedation in a patient with severe respiratory distress.

Chronic pain / Palliative Care

Individual oral dose requirements vary markedly, and patient response should be monitored frequently.

In patients receiving palliative care, large doses may be required to control pain

Initial oral *immediate release* preparation dosing is generally:

Adults: **5- 30 mg orally 4 hourly**

Children: **0.2 to 0.4 mg/kg orally 4 hourly**

Children weighing more than 50 kg are generally considered adults for the purposes of prescribing.

Factors to consider when converting from immediate-release to **modified-release** opioid preparations: [1]

- Determine the dose required over the 24-hour period (the sum of all regular and breakthrough opioid doses - exclude those used for incident pain - given in the previous 24 hours).
- For preparations given twice daily, give half of the calculated total daily dose 12-hourly.
- For preparations given once daily, give the total calculated daily dose at the same time each day.
- Give the first dose at the same time as the last dose of immediate-release opioid to allow for its slow onset of action. (This method need not be used with modified-release oxycodone, which already has an immediate-release component.)
- Continue access to breakthrough dosage

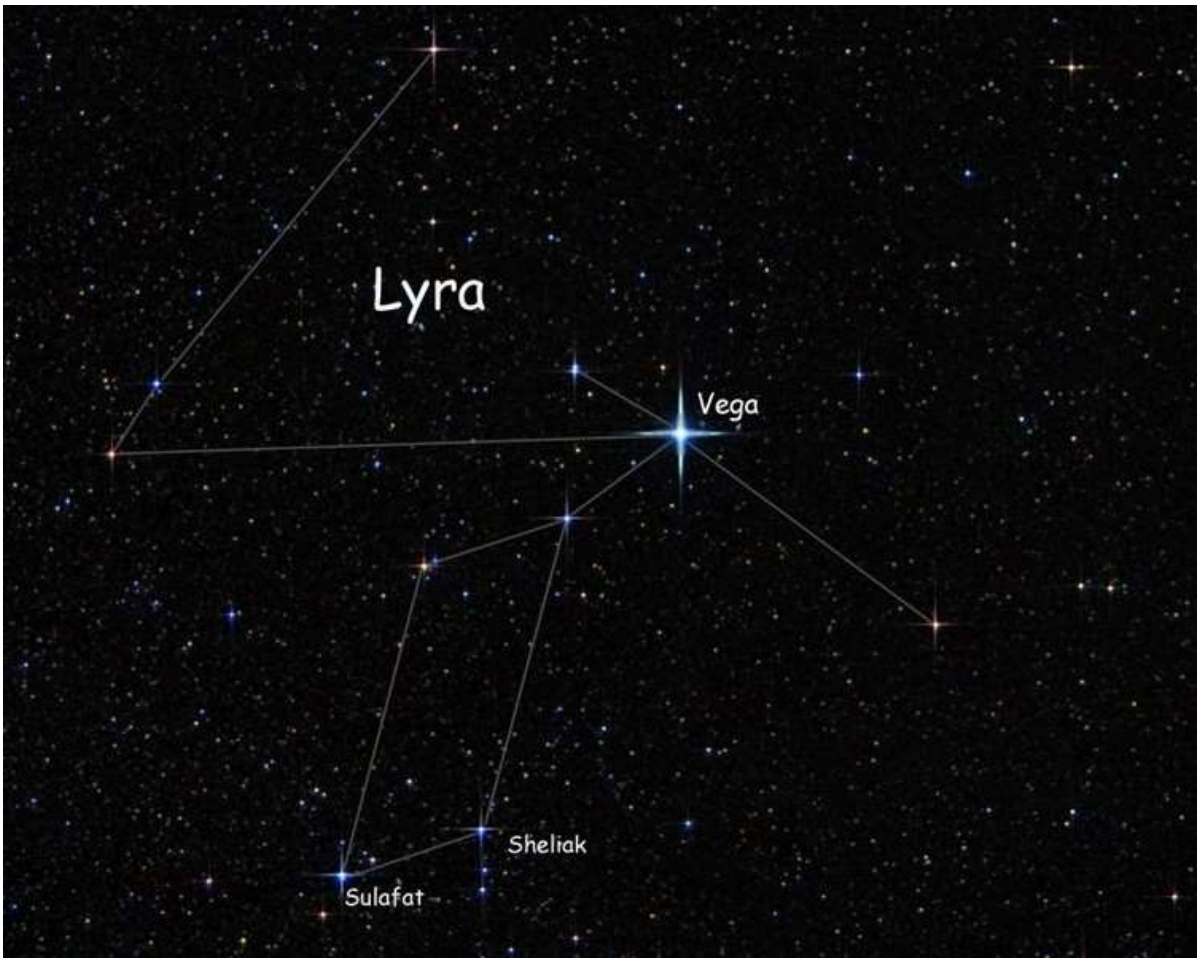
See also Latest Palliative Care Therapeutic Guidelines

Antidote:

Naloxone is the specific antidote for opioid toxicity/ overdose

See also separate Document, Naloxone (in Drugs Folder).

“Dead Orpheus”, oil on canvas, 1893, Jean Delville, (Symbolist).



The Constellation of Lyra - (Astrophotography, Walt Davis)

References

1. eTG - March 2017

2. Morphine in MIMs, Website, Accessed May 2014.

3. Morphine in AMH, (Australian Medicines Handbook), Accessed May 2014.

4. The Acute Pain Management Manual NHMRC, 2011.

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