THE NORTHERN HOSPITAL

OXYCODONE

"Odysseus and Calypso", oil on canvas, 1616, Jan Brueghel the Elder. "...he slept with her in her cave, but there was no choice; she was passionate, and he had to".

All the Achaeans who had survived the war and the voyage home had long since returned to their houses. That man alone still longed for his land and his wife; the beautiful nymph Calypso was keeping him inside her cavern, wanting to make him her husband…

Homer, "The Odyssey" Bk 1:14-18, c. Eighth century, B.C

…Hermes did as Zeus commanded….he skimmed the water like a seagull hunting for fish as it dives through the dread troughs of the waves and moistens its wings in the spray. But when he came to the island that lay far off in the midst of the violet sea, he landed and walked until he came to the cavern were the nymph lived.

He found her at home. A fire burned on the hearth, and the scent of cedar and juniper spread far out over the island. Inside Calypso was sweetly singing as she moved back and forth at her loom and wove with a golden shuttle. In front of the entrance a luxuriant wood grew: alders, poplars, and fragrant cypresses, where many large birds made their nests - horned owls and falcons and loud screeching cormorants, who fly to the sea for their living; and all around the mouth of the cavern, a vine trailed, heavy with grapes. Four clear springs bubbled up there, near one another, and flowed with clear water, then turned off in four directions, and in meadows on either side of them violets bloomed and wild parsley. Even a god who came to that place would marvel, and the messenger Hermes stood there marveling at it.

And when he had looked around to his heart's content, he entered the cave. Calypso knew who he was, gods know each other at once… But he did not find Odysseus inside the cave; he was on the shore, sitting and watching the sea, as he often did, racking his heart with groans and with bitter weeping. Calypso had Hermes sit down…."What brings you here, Hermes? This is an honour!"….the goddess then drew up a table with a large plate of ambrosia on it and mixed him a cup of red nectar and he ate and drank…And when he had finished his meal…he said to her, "Goddess…it was Zeus who sent me, I am here at his command. Zeus tells you to let him go now, immediately. It is not ordained that he spend his life here with you on this island. He is fated to reach his country and finally see his home and the people he loves".

Hearing these words, Calypso shuddered and said, "You are all hard hearted, you gods, and envious too; you hate it whenever a goddess sleeps with a man, even if she has chosen him as her husband…you envy me now for living with a mortal man. I rescued him as he floated alone, astride the keel of his ship, when Zeus had blown it apart with lightning on the dark sea….Yet willingly and with good grace, I promise to do whatever is in my power to send him off on his way to his own dear country"…and at once Calypso set out to look for Odysseus. She found him sitting and weeping on the shore…as he mourned for Ithaca. No longer did the nymph please him. At night, it is true, he slept with her in her cave, but there was no choice; she was passionate, and he had to…

"Noble Odysseus are you really going to leave me now and return to your own dear country? Well I wish you the best. Yet if you had any idea of the hardships you will have to endure before you can ever reach home, you would stay with me here and let me make you immortal, however you long for that wife of yours, whom you think of day in and day out. But I am not any less attractive than she is, surely in face or figure; and indeed it would be unimaginable for a mere woman to come even close to a goddess in beauty".

And Odysseus, the great tactician, answered her, "Goddess, don't be angry. I know as well as you do - that Penelope isn't as tall as you are or as lovely. And, yes she is only a woman, while you are immortal and will never grow old. I know that. Yet even so, I can't help longing for home. And if some god does wreck me during the voyage, I shall endure

it. My heart knows how to endure great hardships. Before now I have suffered many, both on the sea and in war, and if I must suffer another hardship, so be it".

As they were speaking, the sun set and darkness came on. And they moved farther into the cave, and they made love with great pleasure, and then they slept in each other's arms….

Homer, "The Odyssey" Bk 5, c. Eighth century, B.C

Of all the Nereids, or sea nymphs, Calypso was the most beautiful and the most powerful seductress. She was the daughter of the mighty Titan, Atlas, who after the defeat of the Titans in their great battle with the gods of Olympus was condemned to carry the weight of the world on his shoulders. As his daughter, who had not taken sides, the gods were lenient to Calypso, exiling her to the island of Ogygie. The island however was a magical place to live, a paradise on earth, blessed with perpetual birdsong, bubbling crystal clear brooks, towering cypresses and poplar and fields of violets and parsley.

She lived in a large beautifully vegetated cavern, and the air was filled with sweet swelling cedar smoke, juniper and thyme. Even the gods were taken aback when they visited the island of Calypso. But Calypso was lonely and wanted a husband, and so she couldn't believe her luck when a strong bronzed Greek warrior was washed up onto her shores. Odysseus had been on his long journey home when his ship was struck by a terrifying storm. The ship sunk and he was the only survivor. Calypso fed him and nursed him back to health, then proceeded to make love to him.

At first Odysseus could barely believe his luck as well, living on an island paradise with every kind of fruit and game, as well as being the lover of an immortal and passionate goddess. But in the back of his mind he was troubled. Despite his idyllic existence he yearned to see his beloved wife Penelope and his son Telemarchus, who by now must have grown to manhood. But at the same time he could not bear the thought of losing Calypso. So for seven long years he lived with her and loved her. But despite the charms of the goddess, his thoughts and his longing grew steadily more powerful for his homeland Ithaca and his family he had not seen for seventeen years. His passion for Calypso began to wane, and yet she had such a powerful hold over him, he could not leave her.

Odysseus became desperately unhappy, torn between Calypso and his wife Penelope - and increasingly torn with the guilt of his infidelity one suspects. Despite Calypso's escalating efforts to entice him with promises of eternal youth it had become clear to her the Odysseus wanted to go home. Odysseus was no longer the goddesses' willing lover but instead had become a captive on her island. The situation had not gone unnoticed on Olympus. Finally Athena intervened and asked Zeus to command Calypso to release Odysseus from her island, explaining that it was Odysseus' fate to return home, and that Calypso was interfering with the will of the gods of Olympus. Zeus agreed and sent Hermes to command Calypso to release her lover.

Calypso was much distressed at Zeus' command. She angrily accused the gods of hypocrisy, saying that all of the Olympians repeatedly had affairs with mortals. Nonetheless, not wishing to suffer the wrath of the king of the gods, she told Hermes she

would comply and provide Odysseus with the means of returning to Ithaca, Odysseus was delighted that he could finally go home, but when it came for the time to leave he still found it difficult in the extreme. He spent his last night on the island making passionate love to Calypso!

We need be wary of the powerful enchantments of the agent oxycodone. For those who take it in the long term, its charms are most alluring - especially if taken for seven years! A break with it, even though desperately desired, may prove just as difficult as breaking with a goddess. Just as the enchantress Calypso cast her spell over the hapless hero Odysseus ensnaring him in her powerful charms, so oxycodone may cast its powerful spell over those to have a prolonged and unnatural relationship with it!

"Calypso" oil on canvas, 1897, Herbert James Draper

OXYCODONE

Introduction

Oxycodone is a semi-synthetic pure opioid agonist whose principal therapeutic use is for analgesia for moderate pain in both acute and chronic conditions.

It was originally developed in the hope that a thebaine derived opioid would be less addictive than other opioids, though as for any opioid it still retains *significant* potential for addiction and abuse.

Its principle advantage is that it is more consistently metabolized in the liver than is the case with codeine and so has more predictable and reliable clinical effects.

There are **immediate release** and **sustained release** oral preparations.

Oxycodone is mostly used in the oral form, but there is an IV formulation also available.

With regard to IV use in the ED, the main utility could be in situations where a parenteral opioid is required, yet the patient has significant allergy or excessive side effects with the first line agents, morphine and fentanyl. IV oxycodone could be an extra option in these situations.

The antidote for toxicity is, as for all opioids, **naloxone.**

See also separate Documents on:

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

Chemistry

Oxycodone is a semi-synthetic opioid synthesized from the poppy derived alkaloid, **thebaine.**

History

Oxycodone was developed in 1916 in Germany by Freund and Speyer of the University of Frankfurt

It was one of several new semi-synthetic opioids developed in an attempt to improve on the existing opioids.

Oxycodone was synthesized from thebaine a few years after the German pharmaceutical company Bayer had stopped the mass production of heroin due to its hazardous side effects and strong potential for addiction.

It was hoped that a thebaine derived opioid would retain the analgesic effects of morphine and heroin but with less dependence, however as with all opioids, the problem of dependence is still significant.

It was first introduced to the US market in May 1939.

Preparation

Immediate release oral preparations:

- **Oxynorm** and **Endone** are commonly prescribed immediate release tablet preparations.
- Tablets are generally of **5 mg.**
- There is an oxynorm **liquid** preparation; **1 mg/mL**

Sustained release oral preparations:

- **Oxycontin** is an oral modified-release formulation that is **biphasic** and provides early onset of analgesia at **one hour**, and a more prolonged duration of action lasting **12 hours**.
- A range of dose preparations are available, including, **10, 15, 20, 30, 40, 80 mg.**

Suppository:

- **Proladone** is a **30 mg** formulation of oxycodone that can be given rectally.

Oxycodone - Naloxone combination oral preparations:

- **Targin** is an oxycodone - naloxone preparation that is used when constipation is a particular problem.

Ampoules:

There is an IV preparation of oxycodone (oxynorm IV) available - but in Australia this is uncommonly used in the ED.

- **10 mg/mL, 1 mL, 2 mL**
- **50 mg/mL, 1 mL (for infusion only)**

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

Oxycodone is an opioid agonist and binds to mu and more weakly to kappa and delta opioid receptor subtypes.

Pharmacokinetics

Absorption:

- Oxycodone is usually given orally.

  It is well absorbed from the gastrointestinal tract.

  Oxycodone is one to two times as potent as morphine when given orally, (because of its higher bioavailability)

  It has similar onset, duration of action and effectiveness in equianalgesic dosing to oral morphine

  Following oral administration of oxycodone tablets, analgesic effect occurs within **10 - 15** minutes and reaches a maximum at **30 - 60 minutes.**

  Effect persists for 3- 6 hours in non-tolerant patients.

- There is a suppository form (Proladone).

- ♥ Suppositories have slower onset of action and a longer duration of effect than conventional oral tablets.

- There is also an IV form (oxynorm IV)

Distribution:

- Oral bioavailability is up to 90% , (greater than oral morphine).

Metabolism and excretion:

- Oxycodone is extensively metabolised in the liver.

  It has two metabolic pathways.

  - ♥ Via the cytochrome P450 isoenzymes:

    - ♥♥ **Noroxycodone** is the principal active metabolite (by N-demethylation) but it has only *weak* affinity for the mu-opioid receptor.

  - ♥ Via the CYP- 2D6 enzymes:

    - ♥♥ **Oxymorphone** is the metabolite here. It is not thought to contribute significantly to analgesia.

  It is the **parent oxycodone** compound that contributes the major portion of analgesic activity.

  Both metabolites then undergo glucuronidation and are excreted together with some unchanged drug in urine.

- The elimination half-life of oxycodone is reported to be 2-4 hours.

While there is *some* variation in the rate of metabolism of oxycodone amoung individuals, this is not nearly to the same extent as that seen with **codeine.**

Pharmacodynamics

Opioid receptor binding by oxycodone in the central nervous system (CNS) produces analgesia with some associated sedation.

Additional pharmacologically mediated effects of oxycodone involve the CNS, smooth muscle and cardiovascular system.

Indications

Analgesia for moderate to severe pain in both acute and chronic conditions.

Contraindications/ Precautions

These include the usual opioid 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)

4. Renal impairment, (relative contraindication):

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. Known hypersensitivity to oxycodone.

Pregnancy

Oxycodone is classified as a class C drug with respect to pregnancy.

Class 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. Specialized texts should be consulted for further details.

Breast feeding

Compatible in **occasional** doses; observe infant for sedation. [1]

Adverse Effects

Adverse effects are those of all opioids in general and so 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.
  - ♥♥ In general semi-synthetic opioids also tend to be less constipating, than the natural opioids, although this is *highly patient dependent.* [1]

4. CVS:
   - Hypotension, though this is minimal with *oral* oxycodone.
   - It can potentiate the action of hypotensive agents.
5. Allergic reactions:
   - Note hoverer that semi-synthetic opioids such as oxycodone generally cause *less* histamine release and therefore produce less vasodilation, flushing, itching and/or rash, than is seen with the natural opioids. [1]
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

Oral:

Oxynorm:

- **Oxycodone immediate release: 5 - 10 mg orally 4 - 6 hourly PRN** [5]

  For moderate pain in patients who are opioid naïve, start with 5mg oxycodone.

  If this is tolerated, but there is an inadequate response, a further 5 mg may be given after 30 - 60 minutes.

  Larger and more frequent doses may be necessary.

  Failure to respond to oxycodone may be an indication to prescribe titrated IV morphine.

Oxycontin:

- **Oxycontin** is an oral modified-release formulation that is **biphasic** and provides early onset of analgesia at **one hour**, and a more prolonged duration of action lasting **12 hours**. It is given **12 hourly.**

Rectal:

- Adult, 30 mg every 6 - 8 hours as required.

  Use caution in opioid-naive or elderly patients due to the risk of toxicity because of the strength of this formulation. [2]

  Suppositories have slower onset of action and a longer duration of effect than conventional oral tablets.

IV:

- This is generally given as **1-5 mg IV** 4 hourly (but higher doses may be required). [4]

  Doses of more than 5 mg may cause significant sedation and respiratory depression if given as a *single* IV injection. [4]

Dilute to 1 mg/mL in 0.9% saline or 5% dextrose.

For infusions:

- Dilute the 50 mg/mL ampoule to 50 mL with a compatible fluid to make a concentration of 1 mg/mL. Start the infusion at 2 mg/hour [4]

IV oxycodone is uncommonly used in the ED. It is more commonly used in the setting of anaesthetics/ operating theatre.

IV oxycodone has a number of advantages over morphine, however it also has some drawbacks as well, which can be summarized in the comparison (to morphine) table below:

Parameter	**IV Oxycodone**	**IV Morphine**
Staff familiarity	Much less	Very high
Cost	About twice as much as morphine	Less expensive
Addiction	Oxycodone has great addiction potential, and so is less suitable in patients *already dependent on oxycodone*	Also has significant addiction potential.
Sedation	Possibly less sedation than that seen with morphine	More sedating
Weaning	Will allow for easier weaning onto oral oxycodone. *	Weaning to oral oxycodone more difficult with regard to establishing optimal dosing.
Onset	Quicker onset of action	Slightly longer onset of action.

Potency	Both agents provide similar levels of analgesia. 1 mg of **IV** oxycodone is equivalent to 1 mg of **IV** morphine

** Transferring patients between oral and parenteral oxycodone*: [4]

- The dose should be based on the following ratio: 2 mg of oral oxycodone is equivalent to 1 mg of parenteral oxycodone.

  It must be emphasized that this is only a guide to the dose required. Inter-patient *variability* requires that each patient's dose is carefully titrated to their clinical response.

With regard to use in the ED, the main utility could be in situations where a parenteral opioid is required, yet the patient has significant allergy or excessive side effects with the first line agents, morphine and fentanyl. IV oxycodone could be an extra option in these situations.

Antidote:

Naloxone is the specific antidote for opioid toxicity/ overdose

See separate Document, Naloxone (in Drugs Folder).

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