Opioid Pharmacology

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Introduction

• The available opioids and routes of administration - oral bioavailability

• Practical applied pharmacology - opioid receptors, where they are, dose response curves - agonists, antagonists and partial agonists

• Why are the opioids addictive?

• Side effects

• Why do opioids cause respiratory depression?

• And what to do when it happens

• Pharmacogenetics, pro-drugs, metabolism, tramadol
Overview

Naturally occurring opioids - from the opium poppy
  Morphine
  Codeine (weak)

Simple chemical modifications (1900s)
  Diamorphine
  Oxycodone
  Dihydrocodeine

Synthetic Opioids (1950s on)
  Pethidine
  Fentanyl
  Alfentanil
  Remifentanil

Synthetic Partial Agonists
  Buprenorphine

Antagonists
  Naloxone
Routes of Administration

- Pharmacokinetics
- Oral
- Bioavailability

- First pass metabolism by the liver
  50% of oral morphine is metabolised by first pass metabolism - so give half the dose if giving it parenterally (s/c, IM, IV etc.)

- 10mg orally is equivalent to 5mg parenterally

- Single dose of morphine lasts for about 3-4 hours

- Slow release preparations for chronic pain - MST Continus - twice a day
Routes of Administration

• Parenteral:
  - Sub-cutaneous
  - IM
  - IV

Which will be the fastest?

• IV PCA
  (Patient Controlled Analgesia)

• Epidural / CSF

• Trans-dermal patches for lipid soluble drugs - fentanyl
Short history of the opioids

- Papaver somniferum
  The ‘sleep-bringing’ poppy

- Opium contains morphine and codeine

- Morpheus - greek god of sleep

- The only effective analgesic until about 100 years ago - evidence of opium cultivation going back at least 5000 years
Papaver somniferum

Morphine, codeine - analgesics
Converted to Heroin
Papaverine, converted to verapamil for angina and supraventricular tachycardia
Morphine

- 1806 - pharmacist Friedrich Sertturner
- One of the first plant alkaloids to be purified and quantified
- Raw opium resin contains up to 25% morphine
- Serious problems with addiction, the drug companies started trying to develop non-addictive (and non-respiratory depressant) versions of morphine
Diamorphine

- Simple chemical transformation to diacetylmorphine
- More potent and faster acting (crosses the blood-brain barrier quickly)
- Invented by Bayer in 1898 and promoted as an over the counter non-addictive alternative to morphine!
- Named ‘heroin’ after the Greek ‘heros’ defender and protector
- They stopped marketing it in 1910 …
Controlled Drug (CDs) Legislation

- First started in the 1920s
- Current legislation: Misuse of Drugs Act 1971
- Opioids - Class A drugs
- Practical issues:
  Secure storage
  CD books - two signatures needed
- Prescription regulations for TTOs - see BNF
Synthetic and semi-synthetic opioids

- 1911 dihydrocodeine - about 1.5x more potent than codeine
- 1916 oxycodone - developed to try and reduce dependence - about 1.5x as potent as morphine - reformulated in the 1980s as oxycontin (a slow release formulation) and marketed for non-cancer pain in the US - leading to huge problems with addiction - House
- 1939 pethidine - again marketed as being less addictive (it wasn’t!) - and had lots of unwanted side effects
- Modern more specific and potent synthetic variants - fentanyl, alfentanil, remifentanil - use as trans-dermal patches for chronic cancer pain, in ITU and anaesthesia
Practical Pharmacology

• What is the difference between potency and efficacy of a drug?

• What’s the difference between tolerance and dependence?

• Side effects, and why do they occur?
How do Opioids Work?

Pharmacodynamics

Review of pain pathways - opioid drugs simply use the existing pain modulation system

Natural endorphins (endogenous morphine) and enkephalins

G protein coupled receptors - act via second messengers

Inhibit the release of pain transmitters at spinal cord and midbrain - and modulate pain perception in higher centres - euphoria - changes the emotional perception of pain
How do Opioids Work?

Descending inhibition of pain

Part of the fight or flight response

Never designed for sustained activation

Sustained activation leads to tolerance and addiction
Opioid Receptors

• First opioid receptor identified in 1973

• Greek letter μ for morphine

• Soon after, delta and kappa receptors were identified

• More recently the nociceptin opioid-like receptor has been identified

• MOP, KOP, DOP and NOP

• Receptors now sequenced, all vertebrates have copies of the main opioid receptors - unchanged in evolutionary terms for millions of years
Overall view of the $\mu$-OR structure.
Opioid Receptors

• MOP, KOP, DOP and NOP - what do you need to know?

• Aim remains to develop opioid analgesics without the side effects of respiratory depression or addiction

• Kappa agonists cause depression instead of euphoria

• At the moment all the drugs that we use are μ agonists
Potency vs. Efficacy

**Potency**
Whether a drug is ‘strong’ or ‘weak’ relates to how well the drug binds to the receptor, the binding affinity

**Efficacy**
Is it possible to get a maximal response with the drug or not?
Or even if all the receptor sites are occupied do you get a ceiling response?
The concept of full or partial agonists

**Relative potencies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamorphine</td>
<td>5 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Pethidine</td>
<td>100 mg</td>
</tr>
</tbody>
</table>
Graph showing the response to different doses of Morphine and Pethidine.
100% Response

\[ \log [\text{Dose}] \]

Morphine
100% Response

\[
\text{Response} = f(\text{log}[\text{Dose}])
\]

Morphine

+ Naloxone

+ More Naloxone
Tolerance and Dependence

**Tolerance**
Down regulation of the receptors with prolonged use
Need higher doses to achieve the same effect

**Dependence**
Psychological - craving, euphoria
Physical

**Opioid withdrawal**
Starts within 24 hours, lasts about 72 hours
Side Effects
Opioid receptors exist outside the pain system e.g.: digestive tract, respiratory control centre

We can sometimes deliver opioids epidurally, but for the most part we have to give them systemically

- Respiratory Depression
- Sedation
- Nausea and Vomiting
- Constipation
- Itching
- Immune Suppression
- Endocrine Effects

Different patients have quite a range of sensitivity to opioids - start with a small dose and titrate up as necessary
Opioid Induced Respiratory Depression

• Call for help
• ABC
• Naloxone
• IV is fastest route
• Titrate to effect - don’t give it all once - once you’ve injected a drug you can’t get it back!
• Short half-life of naloxone - beware drug addict overdoses in A&E
Respiratory Depression

Naloxone - 400µg per ml
Titrate to effect - dilute 1ml in 10ml saline

One ampoule of a drug is usually about the right adult dose - if you think you need to open more than one - check with a colleague first!
Counterfeit pills found at Prince's home contain powerful opioid fentanyl

- Synthetic drug 50 times stronger than heroin found in dozens of pills
- Mislabelled drugs were found in luggage belonging to late music star

Prince died of an accidental fentanyl overdose at his Paisley Park home on 21 April, according to autopsy results. Photograph: Roberto Schmidt/AFP/Getty Images

Several pills taken from Prince’s estate in Paisley Park after his death were counterfeit drugs that actually contained fentanyl, a synthetic opioid 50 times more powerful than heroin, an official close to the investigation said on Sunday.
Opioid use in Chronic Non-Cancer Pain

RCGP Substance Misuse and Associated Health
Prescription and over-the-counter medicines misuse and dependence

As Opioid Use Soars, No Evidence of Improved Treatment of Pain

Opioids for persistent pain
Summary of guidance on good practice from the British Pain Society
A consensus statement prepared on behalf of the British Pain Society, Faculty of Pain Medicine of the Royal College of Anaesthetists, Royal College of General Practitioners and the Faculty of Addictions of the Royal College of Psychiatrists.


June 2010
Opioid use in Chronic Non-Cancer Pain

• Opioids for non-cancer pain start to lose effectiveness fairly quickly (within weeks)

• In one large study 50% of patients who were on opioids for non-cancer pain at 12 weeks were still on them 5 years later

• Addiction to the drug leads to manipulative behaviour - easy to start, but can be very difficult to get patients off them

• Opioids were marketed aggressively by the drug companies in the US for chronic non-cancer pain in the late ‘90s

• Now a huge problem in the US, and there are more deaths (35 to 54 age group) from prescription opioids in the US than traffic accidents and firearms combined!
Pharmacogenetics

- Codeine is a prodrug - it needs to be metabolised by cytochrome CYP2D6 to work
- CYP2D6 activity is decreased in 10-15% of the Caucasian population
- + CYP2D6 is absent in a further 10% of this population
- Codeine will have a reduced or absent effect in these individuals
- CYP2D6 is overactive in 5% of this population - these individuals may be at increased risk of respiratory depression with codeine
Metabolism

- Morphine is metabolised to morphine 6 glucuronide which is more potent than morphine
- Morphine 6 glucuronide is renally excreted and will build up and cause respiratory depression in renal failure
- Pethidine is metabolised to norpethidine which is epileptogenic and will build up and may cause fits in renal failure
Tramadol

- Tramadol is a weak opioid agonist, slightly stronger than codeine
- Introduced in 1977
- It is also a prodrug - needs to be metabolised by CYP2D6 to o-desmethyl tramadol to be active - and therefore won’t be effective in about 10% of patients
- It has a secondary effect in analgesia as a serotonin and nor-epinephrine reuptake inhibitor
- So it interacts with SSRIs, tricyclic antidepressants and MAOIs, sometimes fatally - take care prescribing it to patients on antidepressants
- Recent increase in the number of deaths associated with tramadol as a substance of misuse - now a controlled drug - and stricter controls on it’s long term prescription
Points to remember:

- Oral bioavailability - 50% for oral morphine
- Titrate the dose to suit the patient
- Potential for respiratory depression
- Potential for addiction - be very careful before starting strong opioids for chronic backache etc.

Thank you