Pharmacokinetics of strong opioids

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What is the difference between pharmacokinetics and pharmacodynamics?
Definitions

- **Pharmacokinetics** = what the body does to the drug. Encompasses absorption, distribution, metabolism and elimination.

- **Pharmacodynamics** = what the drug does to the body eg. Beta blockers lower blood pressure
Principles of pharmacokinetics

- **A** – Absorption
- **D** – Distribution (volume of distribution)
- **M** - Metabolism
- **E** – Elimination (clearance)
What is half life?
Half life \( (t_{1/2}) \)

Time for elimination to be complete will depend on the half life of the drug i.e. the longer the half life the longer the time to elimination. Renal failure may also prolong half life.
Time to steady state (therapeutic levels)

Drugs with a long half life will take longer to reach therapeutic levels i.e. steady state. Some drugs, e.g., digoxin, may require a loading dose.
CSCI vs SC bolus/oral pulse doses

- CSCI ensures a constant rate infusion of drug, the elimination half life is irrelevant unless the infusion is stopped.
What is bioavailability?
Bioavailability (F)

- The fraction of the drug which reaches the systemic circulation
- Parenteral drugs have 100% bioavailability
- It is due to oral bioavailability that differences between oral and IV or SC doses exist
- If a drug has a really poor oral bioavailability it will not be suitable to be given orally

**Eg. Morphine has bioavailability of 50% ie F =0.5.**

This means that only 50% of the oral dose is absorbed and so the dose given must then be twice the SC/IV dose
Absorption

- For all routes other than IV several lipid cell membrane barriers must be crossed before drug reaches circulation.

- Transport mechanisms:
  - Passive diffusion down a concentration gradient i.e. concentration in GIT is greater than in the blood
Facilitated diffusion allows low lipid soluble drugs to be transported across the cell membrane.

- Active transport – against a concentration gradient.
Drug absorption (oral)
Metabolism

- Most small molecules are metabolised in the liver by cytochrome P450. The initial drug is then converted into new molecules.

- First pass metabolism accounts for a loss of drug concentration as the drug is swallowed, enters the GI tract, then enters hepatic portal system through the portal vein and into the liver before reaching the rest of the body. The liver then metabolizes and only some of the active drug gets into the circulation.
Clearance (elimination)

- Drugs are mainly removed by the kidney and liver.
- Small water soluble hydrophilic drugs are usually cleared unchanged by the kidney.
- Lipid soluble drugs are metabolised by the liver and the metabolite is cleared in the urine.
- Clearance is the amount of drug cleared per unit time (L/hr) and can have a renal and hepatic component.
- Clearance is affected by age, renal/hepatic function, disease and drug interactions.
Alternative routes of administration to avoid FPM

- **SL/buccal/nasal** – rapid onset of action
- **Dermal** – useful for lipophilic drugs
- **Rectal** – only inferior+middle haemorrhoidal veins bypass HPC
- **IM** – influenced by vascularity of site (arm>thigh>gluteus maximus)
- **SC** – slower than IM but less painful
- **IV**
Morphine

- Bioavailability 15-64% This means that about half the oral dose is active systemically and explains why we need to give twice as much orally vs SC.

- Once absorbed goes through FPM and this is why the oral bioavailability is reduced.

- Hydrophilic opioid and levels highest in liver, kidney, lung.

- The BBB controls entry to CNS and in fact if administered directly intraventricularly potency is increased by 900 times.
Morphine

- Excretion via kidneys

- Metabolism is by the liver mainly to Morphine 3 glucuronide (10-15%)

And

Morphine 6 glucuronide (55-80%) active

- Binds to opioid receptors and contributes to both analgesia and side effect profile such as N&V, sedation and respiratory depression

- The half life of M6G is increased from about 2.5hr to 7.5 hrs if patient’s renal function deteriorates and so needs to be avoided or dose/frequency reduced.
Diamorphine

- Bioavailability essentially zero so not given orally as the amount absorbed would be zero
- Prodrug of morphine, it is 100% absorbed orally but 100% metabolised by FPM in the liver
- Undergoes complete biotransformation to 6-monoacetylmorphine (6-MAM) then to morphine...
Oxycodone

- Bioavailability 60-87% so again as per morphine the oral dose is twice as much as SC
- Half life = 3.5hrs, 4.5hrs in renal failure
- Biotransformed by CYP2D6 to oxy-morphone (active) and noroxycodone
- Oxymorphone is 10 times more potent than oxycodone but the percentage is so small that clinical effect is small.
Oxycodone continued

- Oxycodone in the form of Longtec and OxyContin have biphasic release - this means there is a slight peak effect in the first 2-3 hours followed by a constant release.

- NB for newer generic sustained release oxycodone preparations are not biphasic.
Fentanyl

- Oral bioavailability is less than 2% so we do not give orally
- Bioavailability 50% OTFC and 92% TD
- $T^{1/2} = 13-22$ hours (TD) - implications clinically
- Hepatically metabolised to norfentanyl and despropionfentanyl (inactive)
- ~7% excreted unchanged in urine
Fentanyl continued

- Fentanyl is very lipophilic and diffuses into CNS hence blood concentrations are relatively low.
- Saturation of enzymes may occur after repeated doses
- Lipophilicity is the reason that fentanyl is thought to cause less constipation
Alfentanil

- Bioavailability orally unknown and not used orally
- Half life = 40-137 mins (mean 80 mins)
- Liver metabolism and some biliary conjugation + excretion
- Effects prolonged and enhanced in severe liver dysfunction (free fraction)
- Very lipophilic like fentanyl and crosses BBB quickly. Saturation may occur again
- Duration of action very short and hence why it's not always ideal for BT but good for incident pain.
Any questions?