Opioid Equianalgesia

Introduction

• Opioids are the mainstay of pain management in patients with cancer
• Morphine is considered first choice opioid:
  - familiarity
  - low cost
  - available formulations
  - proven effectiveness

• Up to 30% of cancer patients show poor responsiveness to a given opioid such as morphine
• Up to 40% of patients required a change to a different route and/or opioid:
  - administration issues
  - adverse effects
  - lack of effect

 Introduction


• Reasons for opioid switching include:
  - intolerable adverse effects limiting dose escalation
  - inadequate response, despite escalation of current opioid
  - renal/hepatic impairment
  - development of analgesic tolerance
  - patient factors

Opioid Switch

Opioid Switch

• No randomised controlled trials have investigated the efficacy of opioid switching
• Recommendations are derived from retrospective or observational studies
• Satisfactory pain control and reduction in adverse effects after opioid switching has been reported in 50-90% of patients

Opioid Switch

Opioid Switch

• Multicentre, randomised, four-arm, controlled, phase IV clinical trial
• Opioid was switched in 79 patients (15.9%) 87 times, for:
  - uncontrolled pain (53.3%)
  - adverse effects (22.1%)
  - both of these (4.8%)
  - dysphagia (20.8%)
Opioid Switch

Opioid switching and variability in response in pain cancer patients

- Oxycodone resulted in the lowest need for switching solely for uncontrolled pain
- Transdermal opioids were changed more often for uncontrolled pain
- Morphine was substituted similarly for both uncontrolled pain and adverse reactions
- Approx 50% response rate to opioid switch

Defining Pain Management

Opioid responsiveness:
- The degree of analgesia achieved as the dose is titrated to an endpoint defined either by intolerable side effects or the occurrence of acceptable analgesia

Opioid tolerance:
- Is a decrease in opioid responsiveness following repeated or prolonged drug administration
- Characterised by escalating dose requirements to maintain central effects (i.e. analgesia)
  - Tolerance to peripheral effects is very slow or does not occur (e.g. loperamide)
- Complex interplay of many systems involved

Analgesic potency:
- The intensity of analgesic effect for a given dose after binding to a receptor
- The smaller the dose to produce a given effect, the more potent the drug

Relative Potency:
- Defined as the ratio of opioid doses necessary to obtain roughly equivalent effects
- Relative analgesic potency can be determined through controlled clinical trials that compare different drugs or routes of administration
- Historically, 10 mg of parenteral morphine has been considered to be the standard comparator
Potency of a drug relies on its ability to bind to a receptor.

Several factors affect the ability of the opioid to access/reach the receptor.

Equianalgesia, or equipotency, can be achieved by accounting for these factors:
- dose corrections
- alternate route of administration

Equianalgesic dose:

The dose at which two opioids (at steady state) provide approximately the same pain relief.

Two opioids can be made equipotent, resulting in equianalgesia.

Equianalgesia Tables: Are They All Equally Dangerous?

Equianalgesic Tables: Are They All Equally Dangerous?

Opioid Equianalgesic Tables: Are They All Equally Dangerous?

Opioid Rotation: The Science and the Limitations of the Equianalgesic Dose Table

Opioid Rotation: The Science and the Limitations of the Equianalgesic Dose Table

- Identified wide and clinically important differences in published opioid equianalgesic ratios.
- Equianalgesic tables:
  - are derived largely from single-dose studies, expert opinion, and studies in non-cancer patients.
  - should represent a first step in the clinical decision.

- Studies used to develop equianalgesic tables did not assess many of the potential influences on potency.
- Studies of relative potency have largely:
  - included populations with little prior opioid exposure.
  - been single-dose studies.

- Large individual variation in opioid responsiveness leads to incomplete cross-tolerance.
  - not accounted for in tables.
Practical management of opioid rotation and equianalgesia.

- Opioid switch relies on “expert-validated” equianalgesia tables
- Use of adjuvant analgesia on opioid equianalgesia is unknown, but “an impact is highly probable”
- Ratios used are primarily based on old data
- Equianalgesic ratios are not always bidirectional

Pharmacokinetics

- **Bioavailability** is the fraction of the administered dose that reaches the systemic circulation in the unchanged form after absorption
- Reasons of incomplete bioavailability are:
  - inability of the drug to be released completely from dosage form
  - chemical destruction at the site of absorption (e.g. gastric acid)
  - metabolism or excretion by the liver before drug can reach the general circulation (first pass effect)
  - transport (efflux) proteins

**Example**

- Morphine:Oxycodone
- Is oxycodone more potent than morphine?
- No – it isn’t. Parenterally, considered equipotent

**Pharmacokinetics** describes the rate and manner that a drug is absorbed, distributed and eliminated.
*In other words, what the body does to the drug*
Example

PO bioavailability:
- Morphine displays wide inter-patient variation
  - 15-69%, with an average value of 40%  
  - Oxycodone 50-69%; average value of 60%
- Napp maintains 2:1 M:O
- EAPC, BNF, PCT's suggest 1:5:1 M:O

Pharmacokinetics

• TPs are membrane-bound proteins
• P-glycoprotein (P-gp) is an efflux transporter
  - Removes drugs absorbed back into the gut lumen
  - Maintains the integrity of the blood-brain barrier
• Involved in the ADME of several opioids
  - Morphine, loperamide, methadone
  - Oxycodone, fentanyl, hydromorphone, alfentanil (role unclear)

Pharmacokinetics

• Activity of TPs is influenced by:
  - Genetic factors
  - Drugs
  - Foods
  - Inflammatory mediators

Pharmacokinetics

• Transdermal drug delivery – wide interpatient variability in absorption
• Factors such as:
  - Heat
  - Low body weight – cachexia
  • Possibly linked to low albumin, or albumin leaking into extravascular space
  • If essential to use TD fentanyl in cachexia, caution should be taken if the decision is made to switch

Pharmacokinetics

Metabolism – Phase I

• A polar functional group added to form a substrate for subsequent metabolic handling
• Main pathway involves the cytochrome P450 (CYP450) system
• Only four account for over 90% of opioid metabolism:
  - CYP3A4/5
  - CYP2C9
  - CYP2B6
  - CYP2D6

Pharmacokinetics

• First pass metabolism is the loss of drug before it enters systemic circulation
• Cytochrome P450 enzymes line the gut wall and are present in hepatocytes
  - CYP3A4 mainly
• Explains why some drugs inactive orally
  - e.g. fentanyl
• First pass metabolism, phase I & II susceptible to:
  – Drug/food inhibition/induction
  – genetic variation
  – clinical significance less clear for Phase II

Implications:
• Inhibition or induction of TPs can influence:
  – absorption (bioavailability)
  – distribution (BBB)
• Chronic administration of morphine and oxycodone has been shown to upregulate P-gp
  – may have an effect on tolerance development

Pharmacodynamics
• Describes the effect of the drug and how it works in terms of its interaction with a receptor or site of action.
  – In other words, what the drug does to the body
• Clinically used opioids induce analgesia through activation of MOPs
Pharmacodynamics

• This simplistic view of opioid-MOPr interaction is incorrect, or at least incomplete.
• Opioids do interact with other receptors apart from the MOR to produce analgesia (1).


Pharmacodynamics

• Each opioid at MOR interacts in different way, which in turn alters the nature and balance of the responses elicited by its activation.
• Opioid analgesic drugs may elicit very different intracellular responses:
  – may ultimately have very different outcomes on analgesia, addiction liability, respiratory depression, constipation
  – Known as ‘ligand bias’

Implications:

• May be one of several reasons for incomplete cross-tolerance.
• May explain:
  – bidirectional equivalences
  – basis of opioid-combination analgesia

Pharmacodynamics

• Implies that the analgesic effects of these drugs, as well as their AEs, may not be dependent solely on their receptor binding affinity.
• ‘Weak’ vs ‘strong’ opioids in terms of analgesia less definitive than previously thought:
  – tapentadol weak opioid/strong analgesic.

Pharmacodynamics

• Pharmacogenetics is the study of how variation in an individual gene affects the response to drugs which can lead to adverse drug reactions, drug toxicity, therapeutic failure and drug interactions.
Genetic variability can affect an individual’s response to drug treatment by influencing pharmacokinetic and pharmacodynamic processes, e.g.
- Transport proteins
- Cytochrome P450 isoenzymes
- Drug receptors

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Clinically significant drug-drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review

- Main opioids identified were metabolized by CYP3A
  - fentanyl, methadone, oxycodone
- Precipitant drugs added to treatment:
  - fluconazole, clarithromycin
- Discontinuation of a CYP3A4 inducer:
  - carbamazepine

**Drug Interactions**

Oxycodone

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<td>Oxymorphone</td>
<td>(≥4x stronger)</td>
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Effect of inhibition of [CYP2D6] and [CYP3A4] on the pharmacokinetics of i.v. oxycodone
Grönlund et al., Clin Drug Investig 2011; 31(3):143-53

- DDI's arising from CYP2D6 inhibition alone - minor clinical importance
- Clinically significant interactions may occur if CYP3A4 ± CYP2D6 pathways are inhibited

**Drug Interactions**

- It's not just about whether a drug is inhibitor or inducer
- Midazolam and alfentanil/fentanyl
  - effect of midazolam enhanced
  - may also be pharmacodynamic interaction
- Beware of the straw that might break the camel's back!
The Bottom Line

• Paucity of data relating to chronic dosing
• Studies are heterogeneous
• Stated ratios exhibit wide ranges
• Ratio may change depending on direction of switch
• Watch out for drug interactions

The Bottom Line

• The equianalgesic table is a guideline
• No equianalgesic table, or online calculator, can fully address all clinical factors that influence opioid pharmacology
• Designing a study to adequately address all variables that influence equianalgesia would be extremely difficult if not impossible

The Bottom Line

• Two methods for opioid switch have been suggested
• Webster and Fine\(^1\) suggest a cross-over
  - reduce current opioid
  - gradually titrate new opioid
• Fine and Portenoy\(^2\) report a consensus guideline:
  - calculate analgesic dose as per table
  - reduce calculated dose by 25-50% using clinical judgement
  [NB - not fentanyl or methadone]