Principles and Practice of opioid rotation/switching

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Opioid rotation

- Opioid analgesics are not all the same
  - Pharmacological differences in interactions with individual opioid receptor groups
  - Pharmacokinetic differences

- Opioid rotation can be helpful for
  - Opioid tolerance
    - A systematic review of opioid response after 6 months of therapy in 25 non-randomised case series showed weak evidence of modest analgesic benefit and inconclusive data in regard to improvement in physical function and quality of life (Noble 2011)
  - Management of opioid hyperalgesia
    - as method of opioid dose reduction without losing opioid analgesia
  - Inadequate/failed analgesia e.g., patch adhesion problems
  - Adverse effects
Opioid-induced hyperalgesia

- Long term use of opioid analgesics, especially in large doses, is associated with a number of long term problems including hormone suppression (cortisol, oestrogen, testosterone) and hyperalgesia; a state of nociceptive sensitisation or an increase in pain experience, caused by exposure to opioid analgesics
- Opioid analgesia sometimes cause ‘paradoxical’ pain: as the dose of the analgesic is increased the pain become worse
- The pain experienced can change and become different from the original pain
- Whether this is just a function of tolerance is not known although OIH does not seem to respond well to just a change in opioid. It is better if it can be prevented or opioid-based analgesia is avoided


Principle of incomplete cross-tolerance

- Pasternak 2001
- At least 7 different \(\mu\)-opioid peptide receptors identified as well as \(\kappa, \delta\) and \(\zeta\) receptors
- Each receptor will bind different opioids with different receptor affinity
  - Like having 7 chairs in a room (=receptor type) with 3 being occupied. As each becomes occupied the development of tolerance within that receptor is inevitable over time. If another opioid was used it too might occupy 3 (or possibly more) different receptors producing similar or greater analgesia. As a receptor is vacated then that receptor begins to lose that tolerance and over time can become re-sensitised
Oral Morphine Equivalent Daily Dose (OMEDD)

- Used to define opioid burden by making a clinically-based estimation of an equivalent dose of oral morphine
- BUT there is no ability to calculate an equivalent
- Sources such as the ANZCA Faculty of Pain Medicine app will calculate an OMEDD
  - Examples
    - Fentanyl 25mcg/hr patch equivalent to 90mg oral morphine/d (variable 80-100mg)
    - Oxycodone/naloxone 20/10mg 1 tablet q8hrs =60mg oxycodone/day equivalent to 90mg oral morphine/d
- BUT every patient is different so this is not an exact science and extreme caution has to be exercised!!!

Example: Fentanyl patch adherence
How much of dose is actually being delivered?

<table>
<thead>
<tr>
<th>Score</th>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;90% No lift off skin</td>
</tr>
<tr>
<td>1</td>
<td>75-90% Some edges lifting off skin</td>
</tr>
<tr>
<td>2</td>
<td>50-75% Less than half the system lifting off skin</td>
</tr>
<tr>
<td>3</td>
<td>&lt;50% more than half the patch adhering to skin</td>
</tr>
<tr>
<td>4</td>
<td>Patch detached Patch completely lifted from skin</td>
</tr>
</tbody>
</table>

With permission Sudeep Raj Bista 2015
NB This not an exact science

- Rennick 2016
- Explored different conversion methods by different professional groups

Rotation with dose reduction

- During opioid rotation an attempt to reduce the opioid dose to between 30-60% of original is undertaken
- Trying to reduce to less than 40-100mg/d oral morphine equivalent
  - Because
    - Risks of opioid-dose related death is less at doses<100mg/d (Bohnert 2011)
    - Analgesic tolerance development is reduced with smaller doses
    - Risks of OIH are reduced with dose reduction but a critical dose often needs to be identified (Lee 2011) hence often need for maximal reduction followed by titration to an adequate analgesic level
- Variance in choice of maximum OMEDD in Non Cancer Chronic Pain in different countries (US, UK, Canada, Australia)
- Personally I would suggest:
  - > 40mg should prompt specialist referral (ANZCA FPM 2015)
  - >90mg should be a red flag
  - 90mg is easiest to translate into a prescription dose e.g. 30mg twice day OxyContin® or Targin®, 25mcg/hr fentanyl patch
Difficulties

- Rotation to medications with large interval dose availability e.g. fentanyl patch
  - 12mcg/hr patch equivalent to about 45mg oral morphine
- Possible withdrawal effects
  - Reassure - describe likely reactions (diarrhoea, flushing, lacrimation, sneezing, yawning, sweating) usually self-limiting so don’t over-react
  - Take a single dose of IR opioid
  - Return to see prescriber/GP as soon as feasible. Don’t go to ED unless very severe (abdominal cramping, muscle, bone and joint aches/pains, tremor, anxiety, restlessness and severe mood changes)
  - Provide supply of clonidine for sympathetic AEs

Problem medicines in rotations

- Rotation to medications with dual mode activity e.g. methadone, tapentadol (or tramadol)
  - Methadone
    - has both opioid and NMDA agonist pharmacology
    - has zero order kinetics so accumulation occurs and no OMEDD can be calculated. Often we have to involve AOD specialists to prescribe oral Physeptone®
  - Tapentadol /tramadol
    - has both opioid and noradrenaline reuptake (analgesic) pharmacology proportion of total analgesic effect derived from each mechanism are not well defined.
      - original thoughts were that conversion value was ~0.4
        - i.e. 10mg tapentadol equivalent to 4mg oral morphine.
      - now (post Raffa 2018) I am using conversion factor of 0.1
        - i.e. 10mg tapentadol = 1mg oral morphine
  - Care with rotation to morphine in elderly with any degree of renal impairment because of active morphine metabolites (M3G and M6G)
  - Buprenorphine does not seem to have a hyperalgesic effect
Case Example

- Ms. AJ is a 46-year-old lady with chronic low back pain receiving Targin® (oxycodone/naloxone CR) 40/20mg twice daily but has become increasingly tolerant to this medication after last 18 months of continuous use.
- No other issues in her medical history
- Mental health issues of an anxiety disorder with pain catastrophisation in past but this no longer an issue following attendance at a M/D pain management course
- Only takes a dose of oxycodone IR (5mg Endone®) on rare occasions
  - Her GP limits her to a box of 20 tabs and expects this to last her about 2 months

You plan to rotate to oral morphine to maintain analgesia yet avoid ongoing tolerance (using principle of non-equivalence in opioid rotation)

Dose equivalency

- The range of equivalence of oxycodone to morphine ranges from 1:1 to 1:2.
- Usually use a 1:1.5 equivalence - i.e. 10mg oral oxycodone equivalent to 15mg oral morphine
- Her use of IR oxycodone can be ignored

- Therefore
  - currently taking 80mg oxycodone/day
  - 80 x 1.5 = 120mg/d oral morphine
Clinical assessment

- Patient would be taking more than 100mg/d
- Risks of both over- and under-dosing her for pain management

- I’d suggest trying a dose reduction to 30% of calculated dose
- If 30% given
  - \((120 \times 0.3) = 36\text{mg oral morphine/d}\)
- Suggest rotate to 20mg oral CR Morphine twice daily

Question

- What do you do about the IR oxycodone?
- Leave untouched, remove entirely or change to an oral morphine equivalent?

Break-through, spontaneous and incident pain

- Three forms of break-through pain now identified (Haugen 2010, Davies 2013):
  - Volitional - pain can be anticipated after an activity that can be planned or ‘managed’
  - Non-volitional - spontaneous pain, cannot be anticipated e.g. colicky bowel pain
  - End-of-dose failure - pain occurs after time associated with administration of a CR analgesic

- On discussion with patient her breakthrough pain seems mechanical in nature
  - Breakthrough pain occurs after food shopping when she has to carry a bag from the supermarket back to her car
  - She understands that her breakthrough pain does not represent harm but where she is not ‘mindful’ of what she is doing

- I would suggest that we avoid any IR opioids. In her history her increasing use of oxycodone is associated with a volitional b/t pain type unrelated to her frequency of her CR opioid

- If a breakthrough medication is required then a NSAID such as naproxen 250mg q8hrly prn recommended (more likely to be an inflammatory causation with this type of acute painful flare

- I would ask her GP to continue her IR opioids for a short period over the first week of her rotation. She has confidence in its analgesic activity and this would fine tune her new opioid dose
Personal rotation notes

- Rotation to 'Contin®' CR-mechanism-based products
  - There has been a recognised problem with Contin®-based products.
  - These products do not seem to 'last' for 12 hours i.e. they are often associated with End-of-Dose Failure (Adams 2002, Marcus + Glick 2004, Gallagher, Weiz-Bosna, Gammait 2007) especially in younger patients with Chronic Non-Cancer Pain)
  - Most frequently require q8hrly dosing or occasionally q6hrly
- If Morphine I would suggest using Kapanol® brand
  - Originally designed for once daily but best used q12hrly
- I would usually avoid rotation to
  - Fentanyl patches because of adhesion problems, especially in the heat and humidity of Queensland
  - Hydromorphone CR, because of the seemingly fast onset of tolerance with this opioid

Questions?

- Opioid rotation is less science than ‘art’
- We need to understand that this is not a calculation but a clinical estimate...... Students find this concept particularly challenging
- Plan cross-over knowing about pharmacokinetic/pharmaceutical properties of the first opioid e.g., Fentanyl patch
- Be prepared to get it wrong sometimes!
  - I have three memorable disasters!
- This is NOT ‘Set and Forget’ but ‘Do and Review’
- Educate your patient of your expectations
  - Analgesia should be maintained, essentially unchanged but on potentially a smaller opioid dose. Not looking for ‘pain free’ status but manageable plan
  - Adverse effect spectrum may change e.g., changing from Targin® to morphine may be associated with an increase in constipation and some sedation. You should recommend a suitable aperient to manage this.
References


