Opioid Substitution

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ST6 Palliative Medicine

Aims

- Review indications for opioid substitution and alternatives to opioid substitution
- Review evidence for efficacy of opioid substitution
- Consider factors that affect the choice of the new opioid
- Review the evidence for equianalgesic ratios

Mrs Y

- Advanced gastric cancer
- Multiple admissions to hospice IPU with complex abdominal pain and nausea
- Current opioid is Oxycodone 400mg over 24 hours via CSCI
- Further options for non-opioid analgesia or anaesthetic interventions limited
- Still in pain despite recent escalation in Oxycodone dose, multiple PRN doses of Oxycodone with partial effect, no overt opioid toxicity but drowsy at times

To switch or not to switch??

When is Opioid Substitution Indicated?

What are the alternatives?

When is Opioid Substitution Indicated?

- Intolerable adverse effects limiting dose escalation
- Intolerable side effects developing during continuous use, unresponsive to simple measures such as dose reduction, or dose reduction leads to increased pain.
- Inadequate pain relief despite escalation of current opioid
- Renal or liver impairment
- Change of route required
- For patients on morphine with moderate to severe constipation, despite adequate laxatives, substitution to transdermal fentanyl may be indicated.
- Patient acceptability

What are the Alternatives?

- Reducing the dose of strong opioid.
- Use of appropriate rehydration.
- Use of adjuvant medications to limit side effects e.g. haloperidol for hallucinations.
- Checking for potential drug interactions.
- Use of co-analgesics / interventional pain techniques appropriate to the pain syndrome.

Evidence for efficacy of opioid substitution

- Observational studies showed opioid substitution for inadequate analgesia and or adverse effects had a success rate of between 65-86%
- Patients on corticosteroids significantly less likely to have an opioid substitution in one observational study
- 3 RCTs comparing Morphine and Oxycodone found they are equally effective and well tolerated
- 1 open label RCT found that 95% of pts could achieve adequate analgesia with acceptable adverse effects with either Morphine or Oxycodone
- No studies that compare analgesia and adverse effects between opioid substitution and no opioid substitution

Choosing the new Opioid

- What has already been tried
- Renal function
- Liver function
- Desired route of administration
- Patient preference
- Prognosis
- How well controlled the pain is

Prescribing the new Opioid

- Which equianalgesic ratios should be used?
- What factors should influence the dose of the new opioid?

Equianalgesic ratios

Oral Morphine : Subcutaneous Morphine = 2:1

Oral Morphine : Oral Oxycodone = 1.5:1

Oral Oxycodone : Subcutaneous Oxycodone = 1.5:1

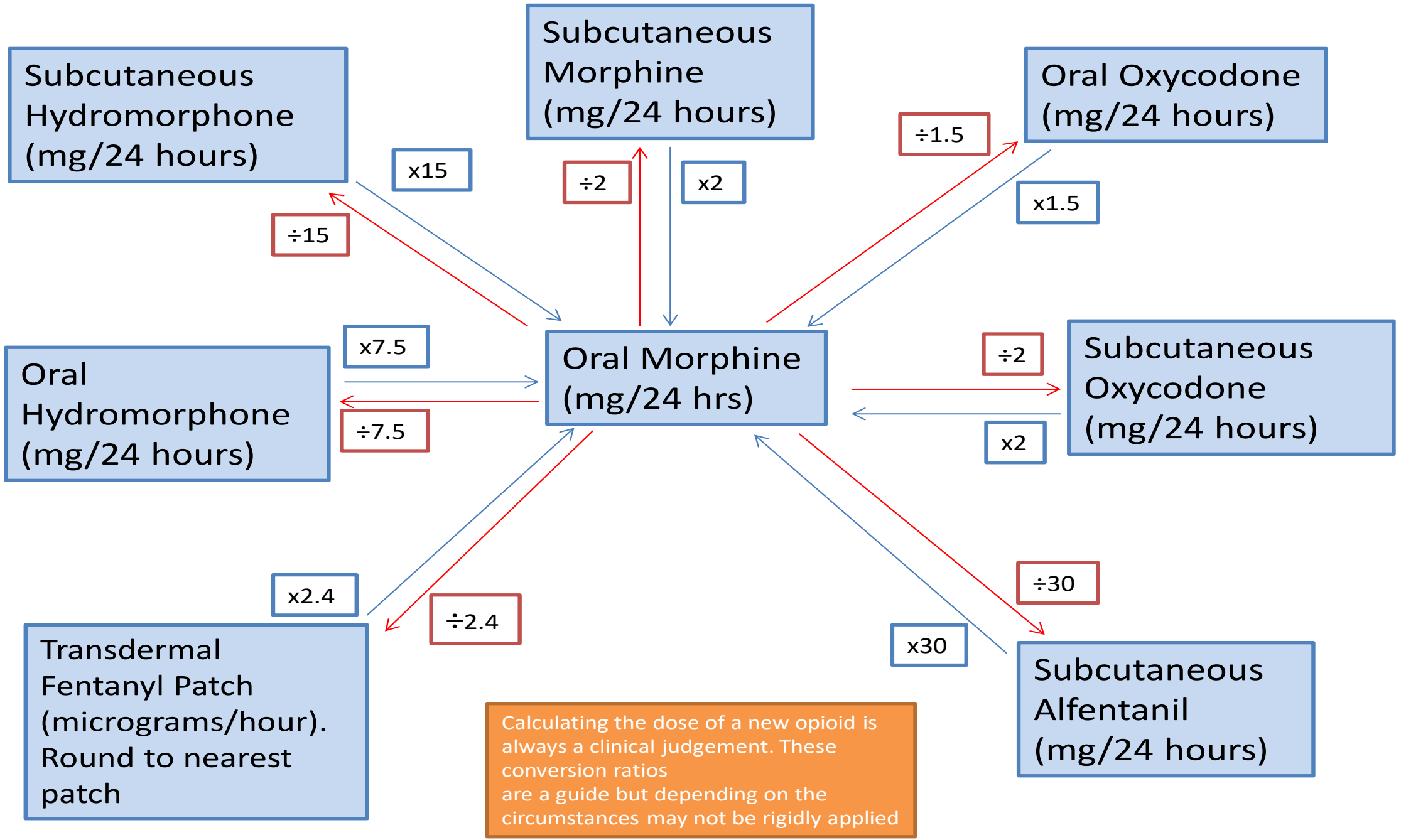
Subcutaneous Morphine : Subcutaneous = Oxycodone 1:1

Oral Morphine : Subcutaneous Alfentanil = 30:1

Oral Morphine : TD Fentanyl = 100:1

Oral Morphine : TD Buprenorphine = 100:1

Oral Morphine : Oral Hydromorphone = 5:1


Subcutaneous Hydromorphone (mg/24 hours)
Subcutaneous Morphine (mg/24 hours)
Oral Oxycodone (mg/24 hours)
x15
÷15
÷2
x2
÷1.5
x1.5
Oral Hydromorphone (mg/24 hours)
Oral Morphine (mg/24 hrs)
Subcutaneous Oxycodone (mg/24 hours)
x7.5
÷7.5
÷2
x2
Transdermal Fentanyl Patch (micrograms/hour). Round to nearest patch
Subcutaneous Alfentanil (mg/24 hours)
x2.4
÷2.4
÷30
x30
Calculating the dose of a new opioid is always a clinical judgement. These conversion ratios
are a guide but depending on the circumstances may not be rigidly applied

Evidence for Oral Morphine to Oral Oxycodone conversion ratios

- **Cross over RCTs**
  - Kalso and Vainio 1990: 20 patients. Initial ratio 1.5:1, final ratio 1.3-1.4:1
  - Heikanen and Kalso 1997: 45 patients. Initial ratio 1.5:1, final ratio 1.5:1 if given Oxycodone first and 1.25:1 if given Morphine first
  - Bruera et al 1998: 32 patients. Initial and final ratio 1.5:1
  - Lauretti et al 2003: 26 patients. 1.8:1
- **Prospective case series**
  - Riley et al 2006: 48 patients. Initial ratio of 2:1, final ratio not reported
  - Narabayashi et al 2008: 27 patients. Initial ratio of 1.5:, final ratio 1:1

PCF 6, BNF and EAPC recommend an oral Morphine to Oral Oxycodone ratio of 1.5:1. SIGN guidelines and manufacturers recommend 2:1

Evidence for Oral Oxycodone to Parenteral Oxycodone and Parenteral Morphine to Parenteral Oxycodone conversion ratios

- Kalso and Vainio 1990
  - iv Oxycodone to oral Oxycodone 0.7:1
  - iv Morphine to iv Oxycodone 0.7:1 i.e. parenteral Morphine *more* potent than Oxycodone

Morphine to Alfentanil conversion ratio

- Retrospective case series
  - Cran et al 2017: 35 patients in two SPC units. Compared patients rotated from various opioids to Alfentanil. Initial conversion ratio of Diamorphine to Alfentanil 7.4:1 at site A and 11.1:1 at site B. Conversion ratio after two days 7:1 at site A and 6.7:1 at site B.

This suggests a conversion ratio for oral Morphine to subcutaneous Alfentanil of approximately 21:1 which differs from current guidelines of 30:1

Oral Morphine to Oral Hydromorphone conversion ratios

- **RCTs**
  - Hagen and Babul 1997: 44 patients. Compared oral Oxycodone to oral Hydromorphone and gave conversion ratio of **4:1** (equivalent to oral Morphine to oral Hydromorphone of **6:1**)
  - Moriarty et al 1999: 100 patients. Conversion ratio of **7.5:1** but original paper not available for scrutiny
- **Prospective case series**
  - Palangio et al 2002: 73 patients. Initial ratio of 5:1 with final ratio of 3.13:1
  - Wallace et al 2008: 148 patients. Initial ratio of 5:1 with 27% requiring up titration post substitution
  - Weinstein et al 2006: 344 patients. Initial ratio of 8:1 but 54% required up titration post substitution
  - Wirtz et al 2006: 50 patients. Initial ratio of 5:1 and final ratio of 3.9:1
  - **Reddy et al 2017: 394 patients. Conversion ratio of 4.6:1**

Enough evidence to change regional guidelines to recommend Morphine to Hydromorphone ratio of 5:1

Incomplete Cross Tolerance

- Significant inter and intra individual variation in the effects of different opioids. Due to differences in bioavailability and receptor affinities.
- The tolerance that develops to the original opioid may not exist to the same extent for the substituted opioid. This is incomplete cross tolerance.
- The extent and significance of incomplete cross tolerance may vary between individuals.
- Cross tolerance for analgesic effects and adverse effects may be independent. An opioid substitution may be successful where there is more incomplete cross tolerance to the analgesic effects than the adverse effects of the new opioid.
- Even in the presence of uncontrolled pain, it may be necessary to reduce the dose of the substituted strong opioid by 25-50% of the calculated equianalgesic dose to adjust for incomplete cross tolerance.

Factors that influence the starting dose of the new opioid

- Accounting for incomplete cross tolerance
- Presence or absence of renal or liver impairment
- Level of pain control
- Presence and severity of existing opioid related adverse effects
- Patients overall condition and functional status
- Co-existing treatments that might impact on pain e.g. radiotherapy, interventional pain procedures
- Potential drug interactions
- Care setting and predicted length of time until next review
- Drug availability e.g. strength and formulation

Opioid Drug Interactions

QUIZ!

1. Which of the following drugs has CNS depressant effects meaning co-administration may add to the CNS depressant effects from opioids?

a) Sodium Valproate

b) Metoclopramide

c) Ondansetron

d) Melatonin

e) Rotigatine

QUIZ!

2. Which opioid increases the risk of bradycardia when co-administered with Beta blockers and Digoxin?

a) Morphine
b) Alfentanil
c) Buprenorphine
d) Oxycodone
e) Hydromorphone

QUIZ!

3. Medications for which long term condition may significantly increase levels of Oxycodone, Alfentanil, Fentanyl and Buprenorphine?

a) Parkinson's disease
b) Idiopathic pulmonary fibrosis
c) Type 2 Diabetes
d) Rheumatoid arthritis
e) HIV

QUIZ!

4. What effect do Phenytoin and Phenobarbitone have on levels of Oxycodone, Alfentanil, Buprenorphine, Fentanyl and Methadone?

a) Increase

b) Decease

c) None

QUIZ!

5. Levels of which of the following opioids may be decreased by co-administration of St John's Wort?

a) Oxycodone
b) Morphine
c) Alfentanil
d) Fentanyl
e) Buprenorphine

QUIZ!

6. Which group of anticancer drugs can increase levels of Oxycodone, Alfentanil, Fentanyl, Buprenorphine and Methadone?

a) Immunotherapy
b) Platinum based chemotherapy
c) Tyrosine kinase inhibitors
d) Aromatase inhibitors
e) Monoclonal antibodies

QUIZ!

7. Which opioid increases a patient's risk of developing Serotonin Syndrome?

a) Hydromorphone
b) Fentanyl
c) Oxycodone
d) Alfentanil
e) Buprenorphine

QUIZ!

8. Which of the following antibiotics may increase levels of Oxycodone, Alfentanil, Fentanyl, Buprenorphine and Methadone?

a) Ciprofloxacin
b) Tazocin
c) Cefalexin
d) Clarithromycin
e) Cefalexin

QUIZ!

9. Which of the following antiemetics may increase levels of Oxycodone, Alfentanil, Fentanyl, Buprenorphine and Methadone?

a) Aprepitant
b) Metoclopramide
c) Cyclizine
d) Haloperidol
e) Ondansetron

QUIZ!

10. Levels of which of the following opioids are NOT increased by co-administration of antifungal medications including Fluconazole, Miconazole, Itraconazole and Ketoconazole?

a) Alfentanil
b) Morphine
c) Oxycodone
d) Methadone
e) Fentanyl

QUIZ!

11. Which anticancer medication may reduce levels of Oxycodone, Alfentanil, Fentanyl, Buprenorphine and Methadone?

a) Tamoxifen
b) Herceptin
c) Enzalutamide
d) Pembrolizumab
e) Fulvestrant

QUIZ!

12. Some members of which class of cardiac medications may increase levels of Oxycodone, Alfentanil, Fentanyl, Buprenorphine and Methadone?

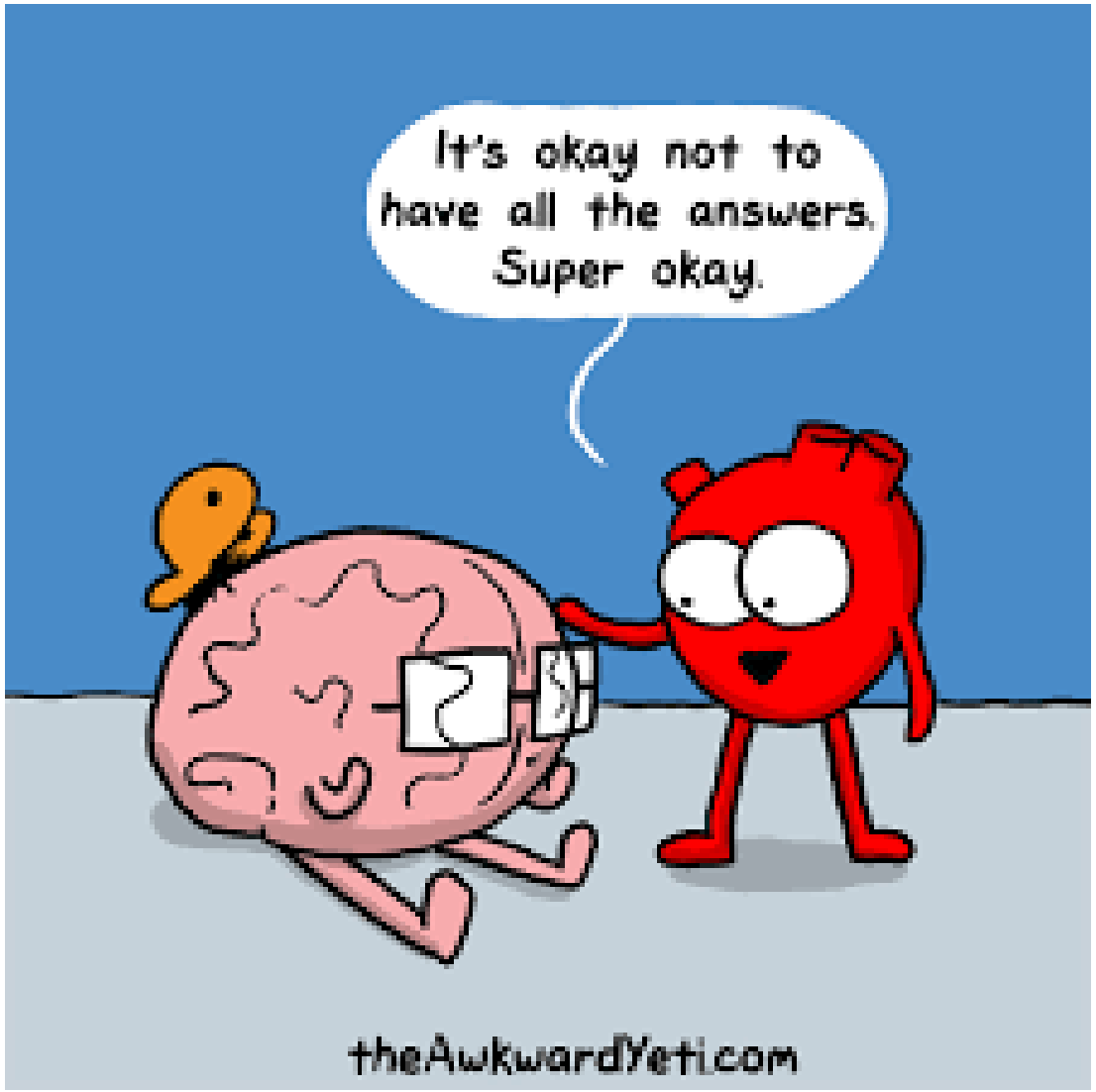
a) Statins
b) ACE inhibitors
c) Loop diuretics
d) Calcium channel blockers
e) Thiazide diuretics

QUIZ!

13. Which of the following opioids increases the risk of prolonged QT interval?

a) Alfentanil
b) Methadone
c) Oxycodone
d) Morphine
e) Fentanyl

ANSWERS


It's okay not to have all the answers. Super okay.
theAwkwardYeti.com

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Cases Studies

Case One

48 year old gentleman with a background of alcoholic liver disease and substance misuse. Has been on Methadone 20mg BD for several years. Admitted to hospital with UGI bleeding, now maximally treated and not for further OGDs.

When you assess him on the gastro ward he is frail, cachectic and confused. The nurses report repeated episodes of haematemesis and that he is struggling with oral medications. You notice myoclonic jerks while you are assessing him but his RR is 18. He appears to be in the last days of life.

He has been on Oramorph 5mg QDS and PRN for abdominal pain. In total over the last 24 hours has had a total of 30mg Oramorph. When you assess him he complains of abdominal pain.

Recent blood tests: Urea 20.2, Creatinine 250, Bilirubin 150, AST, 400, Alk Phos 300, INR 2.9

What drug, dose and route would you recommend for ongoing pain management?

What would you do about the Methadone?

Example Case

Case Two

55 year old lady with breast cancer and bone and liver metastases. She was admitted to the orthopaedic ward four weeks ago after a pathological fracture. Prior to admission she was taking Oxycodone MR 160mg BD. This was converted to Oxycodone 160mg over 24 hours via CSCI shortly after admission due to nausea and has been at a stable dose since. Pain is quite well controlled and only requiring occasional PRN Oxycodone.

Imaging during this admission has shown a progression of liver metastases

Recent bloods: Urea 10.2, Creatinine 95, Bili 50, AST 150, Alk Phos 250, GGT 900

The patient wishes to go back to oral medications as she finds the syringe driver is making it more difficult for her to mobilise

What drug and dose would you recommend switching to?

Example Cases

Case Three

45 year old lady with advanced cervical cancer, admitted to the hospice for management of severe uncontrolled pain. Currently taking Oxycodone MR 30mg BD and Oxycodone liquid 5mg PRN. Taking on average 6 doses of PRN Oxycodone a day with partial effect. On admission reports feeling fatigued and nauseated but not drowsy or confused and no myoclonic jerks. Plan on admission is to arrange for an anaesthetic review with a view to a nerve block

Bloods on admission: Urea 30.4, Creatinine 470, calcium and liver function normal.

USS shows new bilateral hydronephrosis

The patient is awaiting transfer to hospital for nephrostomies to be inserted, condition remains as described above.

What would you do with her opioid prescription?

Example Cases

Case Four

40 year old man with an extensive intra-abdominal malignancy causing inoperable partial small bowel obstruction. Currently managed with a syringe driver containing Oxycodone 60mg and several antiemetics. He is cachectic and having ongoing intermittent episodes of vomiting. He is sipping fluids but not currently taking any oral medications.

The patient is adamant he intends to travel abroad to a developing country in the next few days in order to be with his family when he dies. It is unlikely there will be appropriately skilled healthcare professionals able to manage a syringe driver when he reaches his destination.

Recent bloods: Urea 18.9, Creatinine 150, Bilirubin 45, AST 170, Alk Phos 310, GGT 1500

What drug, dose and route would you prescribe him on discharge for ongoing pain management?

Essential Standards

- The reason for a change of opioid should be documented in the record of care.
- The rationale for the choice and dose of the new opioid, including a dose calculation or reference to a conversion table should be documented in the record of care
- A clear plan for reviewed after an opioid substitution should be documented in the record of care
- The drug brand name should be used when prescribing strong opioids. Please see comments in earlier section

Brand Prescribing

- Included as a standard in regional guidelines after a lively exchange of views
- Some guidelines from NICE and Pan-Mersey pharmacy group that opioids should be prescribed by brand
- However many hospital trusts and electronic prescribing systems will not allow brand prescribing

Mrs Y

Decision made to switch from Oxycodone in CSCI to Alfentanil due to inadequate response to Oxycodone

Conversion 1

Oxycodone s/c 400mg x 2 = Oxycodone oral 800mg
Oxycodone oral 800mg x 2 = Morphine oral 1600mg
Morphine 1600mg / 30 = ***53.3mg Alfentanil***

Conversion 2

Oxycodone s/c 400mg x 2 = Morphine oral 800mg
Morphine 800mg / 30 = ***26.6mg Alfentanil***

Questions?