Pain Control Aims

- General principles of pain control
- Basic pharmacokinetics
- Case history demo
- Opioids –renal failure

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Pain Control

- Morphine is gold standard treatment for moderate to severe pain
- (Klepstad P. Palliat med 2005;19:477-484)
- WHO ladder and guidelines

(WHO Cancer Pain Relief 2nd ed Geneva 1996)

- Morphine been used for 4000 yrs

(Hanks G, Support care Cancer 2005;13: 145-152)

Pharmacological measures

- Successful treatment based on the WHO Analgesic Ladder.
- Regular use of oral morphine has improved the management of pain in advanced cancer.
- Increased use of opioids in non-malignant conditions
- Strong opioids used if pain unrelieved by weak opioids or is severe at outset.
- Oral morphine opioid of choice for severe pain

To achieve Therapeutic Goal

- Knowledge of various formulations

Pharmacokinetics-

- Onset
- Duration of effective analgesia

- Consider patient and clinician preference

- Patient and carer education

Opioid Formulations

- Morphine- MST, Sevredol, Oramorph.
- Oxycodone- Oxycontin, Oxynorm liq/caps
- Hydromorphone- Palladone MR, Pallodone NR
- Fentanyl- Patch, Lozenge, S/L fast acting, Buccal fast acting fentanyl, and Intranasal formulations

WHO Analgesic Ladder

- In line with rising pain intensity increase analgesic drug potency by moving up the ladder.
- Don’t need to start on first step of ladder
- Start on step of ladder corresponding to severity of pain

WHO Analgesic Ladder

Step 1	Step 2	Step 3
Paracetamol	Codeine	Morphine
Cocodamol 8/500	Tramadol	Diamorphine
NSAID	Buprenorphine	Oxycodone
	DF118	Hydromorphone
		Fentanyl
		Alfentanil
		Methadone

Congruence between WHO ladder, Likert and NRS for Pain Intensity Assessment

- Step 1 = Mild = >0-3
- Step 2 = Moderate = >3-6
- Step 3 = Severe = >6-9
- 'Step 4' = Excrutiating = 10 or above

Need to titrate opioids

(a) Opioid-naive patients requiring an opioid (Step1)

(b) Patients no longer responsive to weaker drugs (step 2) requiring strong opioids (Step 3)

(c) Patients on strong opioids requiring higher doses due to an increase in pain intensity or new acute pain

(d) Patients with severe pain due to previous persistent under treatment needing intensive, rapid intervention

Titration

- Initiation of opioid therapy delicate and challenging
- Obtain the maximum benefit and gain patient's compliance.
- Careful balance between rapid pain control and development of adverse effects is imperative.

The use of morphine in poorly pain controlled patients switched from weak to strong opioids

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- Dose titration - use immediate release morphine formulation -rapid onset and predictable effect.
- Give Immediate-release oral morphine every 4 h
- Breakthrough dose of 1/6 of total daily dose of opioid prescribed. Give as often as required.
- Patients changing from weak opioid will usually start with 5mg Morphine four hourly

4 hourly prescribing-IR Morphine

Not 4 times a day!

- 0600
- 1000
- 1400
- 1800
- 2200
- 0200- if awake

Patients changing from weak opioid will usually start with 5mg Morphine four hourly-WHY

- Cocodamol 30/500mg x two tabs QDS
- Equivalent to 240 mg codeine = 24mg morphine. (Morphine 10 x as potent as codeine)
- Tramadol 100mg QDS =400mg tramadol =40mg Morphine. (Morphine 10x as potent as tramadol)

Pharmacokinetics Morphine

- After oral intake immediate release morphine peak plasma concentration in first hour
- Modified release morphine tablets reach peak plasma concentration, after 2–4 h.
- Steady state of morphine reached in about 12-18 hrs.

Overview of Morphine

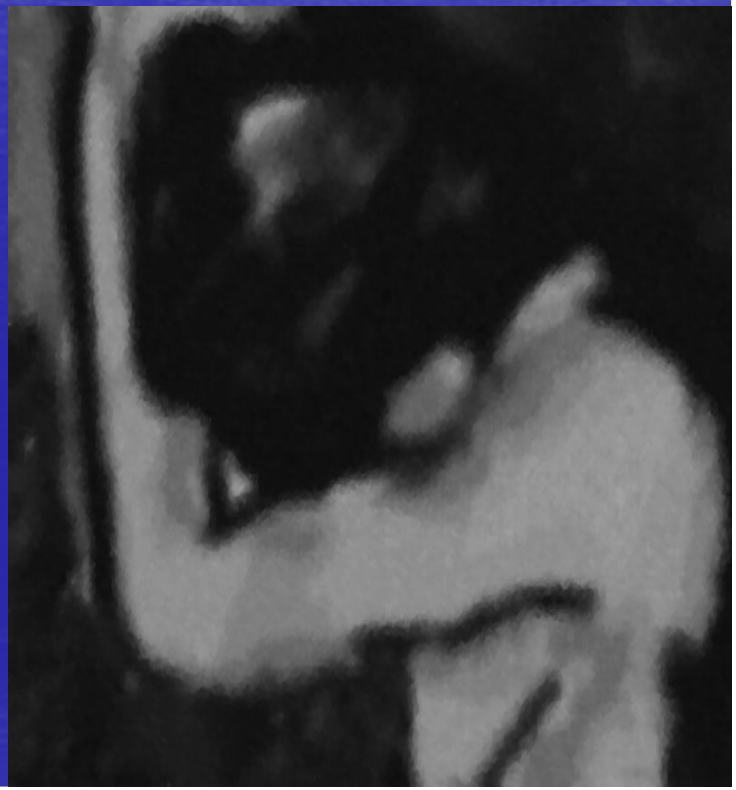
- Preparations - Oral- IR,MR
  - Parenteral IV,SC,IM,IT,
  - PR
- Onset of action - IV 15-30 seconds
  - Oral 15-60 mins
  - IM SC 15-20 mins
- Half –life - 2.2 hrs
- Bioavailability - 20-40%

Opioid side effects – common to all but Intensity varies

- Nausea 30%
- Vomiting 25%
- Drowsiness
- Constipation
- Urinary retention
- Pruritis
- Bronchospasm
- Xerostomia
- Confusion
- Lack of concentration
- Hypotension

Opioid Toxicity

- Vivid dreams
- Pseudo hallucinations – peripheral shadows
- Myoclonus
- Later
- Respiratory depression
- Hypotension
- Bradycardia
- Coma
- Death



Possible outcomes of titrating opioids

- Analgesia is achieved with tolerable side effects
- Before analgesia is achieved side effects limit further escalation of dose
- Pain not controlled despite increasing dose and no significant side effects

Opioid switching

Individual variation in response to opioids:

- Genetic polymorphism
- Physicochemical properties of each opioid
- Psychological factors

Potency/equivalencies of Opioids

Opioid	Potency c/f M	Opioid	Potency c/f M
Codeine	0.1	Methadone	5-10
Oxycodone	2	Fentanyl	100-150
Hydromorphone	7.5	Buprenorphine	50
		Alfentanil	30

Principles of Management of pain

- History -cause, type, severity, holistic

Tools

- Verbal rating score
- Visual analogue score
- Likert scale

- Examination
- Investigation

Treating Background Pain

- Assess severity
- Regular oral analgesia- Around The Clock
- Total daily morphine dose is reviewed daily
- Prescribe correct breakthrough dose (analyse)
- Appropriate adjuvants
- Prescribe a laxative

Case example 1

- 45 year old lady
- Pain left shoulder and radiates down arm
- Lesion brachial plexus
- Mild pain
- Mixed nociceptive and neuropathic
- Prescribed Paracetamol, gabapentin and NSAID

Case example 2

Why Mild pain?

- scored 2/10 and Likert mild

- *Why mixed nociceptive and neuropathic?*
- Descriptors from history
- Neuropathic = Tingling, numb, lancinating, hot, cold, cramp-like, electric shocks

- Nociceptive = Dull, aching, heavy, toothache and radiation

Case example 2- Later

Pain worse 5/10

- Character the same
- Added Cocodamol 30/500 x 2 QDS
- Stopped paracetamol
- Oramorph 2.5 mgs for breakthrough pain

-Low threshold to increase to 5 mg Oramorph

Case example 3

- *Why Cocodamol?*
- Pain 5/10 = moderate therefore = step 2 Analgesic Ladder

- *Why Oramorph 2.5 mgs for breakthrough pain?*
- Cocodamol 30/500 x 2 QDS = Morphine 24mg/24hrs Breakthrough dose 2.5 or 5mg (24/6)
- Never prescribe a range of opioid ie 2.5mg - 5mg. Take the decision

- *Why stopped paracetamol?*
- Each Cocodamol contains 500mg paracetamol

Case example 4 - Later

- Pain score 8/10
- Started on oramorph 5mg x 6 /24hrs
- Plus 5mg oramorph for breakthrough pain
- Gabapentin been titrated to 600mg TDS

Case example 5

- *Why started on oramorph 5mg x 6 /24hrs*
- Pain score 8/10 = Severe pain
- Cocodamol 240mgs /24hrs not effective
- Cocodamol 240 mg= 24mg Morphine
- Want rapid effect for upward titration so use IR Morphine

- *Why 5mg oramorph for breakthrough pain*
- Approx 1/6 of 24 and 5mg oramorph x 6 /24hrs may not be sufficient

Case example 6

- Educate patient and carers
- Allow patient to assess pain severity
- Check response to analgesia
- Frequency dependent upon severity of pain
- Monitor for side effects
- Remember balance vs rapid upward titration to achieve analgesia and increased risk of side effects if dose escalated too quickly

Case example 7 - Later

- Pain responding to new regimen
- Still 6/10 on average and 8/10 at its worst

- *What do you do?*
- Review amount of breakthrough taken in last 24hrs = 5 x 4 = 20mg
- 1/6 of 20 = 3 so new dose of oramorph is 8- impractical so adjust to 10 mg x6 per 24 hrs
- Remember to increase breakthrough to 10mg as needed

Case example 8 - Later

- Pain scoring now 3/10
- Using breakthrough average x1 per 24 hrs
- On oramorph 60mg / 24hrs

- *What do you do now?*
- Convert to Modified Release Morphine
- 60 mg oramorph is = 30mg MST 12 hrly
- Leave oramorph 10mg for breakthrough pain

Omitted?
Laxatives

- Softener & Purgative separately or combined?
- Codanthramer/codanthrusate only for cancer or heart failure patients.
- Senna, bisacodyl, picosulphate purgatives
- Lactulose, dioctyl, movicol softeners

Analgesic Ladder

- 45 year old presents with persistent severe pain scoring 8/10
- Determine cause if possible but may need analgesia before fully diagnosed
- Start on morphine 10 mgs orally x 6
- Can be as oramorph or sevredol
- If in acute distress then parenteral admin required –IV or IM

Message

- Don’t need to start at step 1 of Ladder!

24 hr Oral morphine dose to 24hr parenteral conversion

- On total regular oral dose of morphine of 60mg per 24 hrs. Pain controlled but unable to swallow

- Convert to SC at equivalent dose is 60/2 = 30mg Morphine by MacKinley pump per 24 hrs

Oral to parenteral conversion for breakthrough pain

- IE on sevredol 10mg for breakthrough want to give morphine parenterally
- Morphine orally converting to IV, IM, SC divide oral dose by 2
- Dose is 5 mg

Cautions

Elderly or extremely frail patients eg >75
Multiple co-morbid conditions esp COPD

- Start at lower doses of opioids
- Monitor closely and titrate depending upon response of pain and side effects
- May need only oramorph 2.5 mgs TDS plus same for breakthrough at start

Effect of renal failure on drugs

- Active and toxic metabolites accumulate
- Distribution of drug affected
- Plasma protein binding altered

Protein loss

Uraemia alters binding

Opioids

- Codeine
- Morphine 25-35% protein bound-
- Oxycodone 38% protein bound
- Hydromorphone

Drugs considered safer in Renal Failure

- Alfentanil considered safe for use
- Buprenorphine is generally safe to use in renal impairment
- Fentanyl - Probably safe, at least in the short term
- Methadone - Appears safe

Drugs not to use in >moderate Renal Failure

- Codeine - Do not use.
- Oxycodone
- Hydromorphone
- Morphine - Do not use

Recommended Drugs

- Alfentanil
- Transdermal buprenorphine
- Fentanyl
- Appear to be the safest opioids of choice

Prescribing guidance

- GFR = 90-60 ml/min 100% dose
- GFR = 60-30 ml/min 50%
- GFR = 30-15 ml/min=recommended drugs
- GFR = <15 ml/min = recommended drugs

Conclusions

- If in doubt ask senior colleague
- Opioids safe if used according to guidelines but very dangerous if not
- Contact palliative care pharmacist for advice
- Contact Specialist Palliative Care Team

GFR < 30ml/min greatly increased risk of drug induced toxicity