CLiP

15 minute Worksheet

15 min

Helping the patient with pain

7: Alternatives to morphine

Advanced level

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Aim of this worksheet

To understand what other opioids can be used instead of morphine.

How to use this worksheet

- You can work through this worksheet by yourself, or with a tutor.
- Read the case study below, and then turn to the Work page overleaf.
- Work any way you want. You can start with the exercises on the Work page using your own knowledge. The answers are on the Information page - this is not cheating since you learn as you find the information. Alternatively you may prefer to start by reading the Information page before moving to the exercises on the Work page.
- This CLiP worksheet should take about 15 minutes to complete, but will take longer if you are working with colleagues or in a group. If anything is unclear, discuss it with a colleague.
- If you think any information is wrong or out of date let us know.
- Take this learning into your workplace using the activity on the back page.

Case study

Linda is a 43 year old lady with myeloma. Despite some poor renal function initially, she did well with chemotherapy. Two months ago she relapsed and developed lytic bone lesions. While she was waiting for treatment to take effect she was started on morphine for pain. This worked very well, and she has been on the same dose for several weeks and continued to work. Over the past week, however, she has become increasingly drowsy with pin-point pupils and myoclonic jerks, but remains pain-free.

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INFORMATION PAGE: Alternatives to morphine

Deterioration on a stable dose of opioid

There are five broad possibilities:

- The disease is advancing (unusual over a short time scale, having been relatively well before hand).
- There is a concurrent cause of drowsiness such as hypercalcaemia (common in myeloma) or infection.
- She has taken a higher dose than usual (an error would be the likeliest as suicide attempts with morphine are rare).
- The intensity of pain has reduced in response to treatment e.g. radiotherapy
- She is not eliminating her morphine as efficiently as previously.

The pinpoint pupils, myoclonic jerks and the circumstances of her illness suggest the last cause. One of the active metabolites of morphine is morphine-6-glucuronide (M6G) which is water soluble and excreted by the kidneys. Any change in renal function will make the M6G accumulate. Renal impairment can occur in myeloma (indeed Linda had this problem originally), and a deterioration in renal function with an accumulation of M6G is a likely cause.

Alternative opioids

No strong opioids have been shown to be more effective analgesics than morphine. Morphine, diamorphine and hydromorphone have renally excreted metabolites; methadone and fentanyl do not. Hydromorphone has fewer renally excreted active metabolites than morphine and may be safe in mild to moderate renal impairment, but in severe renal failure fentanyl is the opioid of choice. Oxycodone accumulates in both renal and hepatic impairment. Diamorphine has to be converted to morphine before it can act as an analgesic; it is more expensive than morphine, and apart from greater solubility useful for small volume injections it has no advantages over morphine. Methadone has a prolonged action and should only be used by specialist teams.

1. **F**. IV fentanyl has a short half life, but transdermally it can take up to 14 hours to reach steady blood levels.
2. **T**. Neither of these two opioids are known to have active metabolites that are renally excreted.
3. **F**. A pain unresponsive to morphine is unlikely to respond to these strong opioids.
4. **T**. Fentanyl in the body fat disappears slowly- it can take up to 30 hours for the effects to wear off.
5. **F**. Intranasal administration gives a rapid (within 20 min) rise in fentanyl which would be unsafe in opioid-naïve patients who have not developed tolerance to the adverse effects of strong opioids.
6. **F**. The pharmacokinetics of both make them very difficult to adjust in an ill patient. In addition, diamorphine is converted to morphine, so would be unsuitable for Linda while she has renal impairment.

Steps in starting an alternative opioid

Dose conversion from oral morphine:

Oral Hydromorphone = morphine dose ÷ 5 . Oral Oxycodone = morphine dose ÷ 1.5

Fentanyl: a quick and safe conversion is oral morphine in **mg per 24 hours** ÷ 3 = fentanyl in **microg/hour**

Last dose of morphine:

Hydromorphone: give the first dose of hydromorphone in place of the next controlled-release morphine dose.

Oxycodone: give the first dose of oxycodone in place of the next morphine dose.

Transdermal fentanyl: do not give a controlled release opioid formulation at the same time as starting fentanyl. Instead, a short acting opioid should be continued on an 'as required' basis for at least 12 hours after starting fentanyl to cover the time it takes for fentanyl to reach steady blood levels and to prevent a morphine withdrawal syndrome which can occur in some patients changing to fentanyl (most commonly diarrhoea).

Laxatives:

Hydromorphone and oxycodone: continue the laxatives but adjust the dose to produce a comfortable stool.

Fentanyl: laxatives should be reduced or stopped for 24 hours before starting fentanyl and then retitrated.

Minimum delay between dose increases:

Hydromorphone and oxycodone: can be increased twice daily but are usually increased every other day to allow tolerance to develop to adverse effects.

Transdermal fentanyl: at least 24 hours is needed before the dose can be adjusted.

Influences on the blood levels of the opioid:

Hydromorphone: active metabolites are increased in severe renal failure.

Oxycodone: oxycodone itself is increased in renal or liver impairment.

Transdermal Fentanyl: -increased by thin skin, pyrexia, rashes, or local heat.
-decreased by thick skin or factors causing poor adhesion of patches (eg. hair, sweating)

Choosing the right opioid

Subcutaneous infusion: morphine or diamorphine.

Afraid of using morphine: oxycodone or fentanyl.

Mild - moderate renal impairment: hydromorphone.

Severe renal failure: fentanyl

Liver impairment: morphine (with care).

Stable pain, unable to swallow: SC morphine, diamorphine or transdermal fentanyl

Infection with pyrexia: any opioid can be used except transdermal fentanyl

A postscript on methadone

Methadone is proving to be an interesting opioid which can be useful in patients with escalating pain caused by opioid hyperalgesia (a paradoxical effect of opioids that increases the sensitivity to pain and produces pain that may be different to the original pain, often with hypersensitivity and allodynia). Although methadone has the same potency as morphine, it has a long action and accumulates over several days. Experience has developed special titration regimes which include starting methadone at one tenth of the daily morphine dose. For this reason it should only be used under specialist care or advice.

Think

Think what could have caused her present problems.
Could the morphine be the cause?

True or false?

Since her pain is still responsive to a strong opioid, an alternative opioid could help

1. Transdermal fentanyl has a fast onset of action T F
2. Fentanyl, hydromorphone and methadone are safer than morphine in renal failure T F
3. Hydromorphone, oxycodone and fentanyl could be used for morphine-resistant pains T F
4. In overdose, transdermal fentanyl is more difficult to treat than morphine T F
5. Intranasal fentanyl can be used PRN in a patient on regular paracetamol T F
6. Subcutaneous (SC) methadone and transdermal fentanyl are alternatives to diamorphine SC infusions in the last days of life T F

Write

What steps would you take to convert Linda to an alternative opioid?

	Oxycodone	Hydromorphone	Transdermal fentanyl
What is the dose conversion from oral morphine?			
When do you give the last dose of morphine?			
Should you continue laxatives?			
What is the minimum delay before increasing the dose?			
What might affect the blood levels of the opioid?			

Choose

Which opioid(s) would you choose in the following situations?

Subcutaneous infusion =

Renal impairment =

Stable pain, unable to swallow =

Liver impairment =

Afraid of taking morphine =

Infection with pyrexia =

FURTHER ACTIVITY: Alternatives to morphine

In your clinical practice, review why patients are on opioids other than morphine.

FURTHER READING: Alternatives to morphine

Journal articles

Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clinical Journal of Pain*. 2008; **24**(6): 479–96.

Clark AJ. Ahmedzai SH. Allan LG. Camacho F. Horbay GL. Richarz U. Simpson K. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain.Current Medical Research & Opinion. 2004; 20(9): 1419-28.

Fallon M, Cherny NI, Hanks G. Opioid analgesic therapy. In: *Oxford Textbook of Palliative Medicine* 4th ed. Hanks G, Cherny NI, Christakis NA, Fallon M, Kaasa S, Portenoy RK. eds. Oxford : Oxford University Press, 2010, p661-98.

Hanks GW, et al. Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. British Journal of Cancer. 2001; 84(5): 587-93.

Kirvela M, Lindgren L, Seppala T, Olkkola KT. The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. Journal of Clinical Anesthesia. 1996: 8(1):13-8.

Lee MA, Leng ME, Tiernan EJ. Retrospective study of the use of hydromorphone in palliative care patients with normal and abnormal urea and creatinine. Palliative Medicine. 2001: 15(1):26-34.

Mazoit JX, Sardouk P, Zetlaoui P et al. Pharmacokinetics of unchanged morphine in normal and cirrhotic patients. Anaesthesia and Analgesia, 1987; 66: 293-98.

Mannino R. Coyne P. Swainey C. Hansen LA. Lyckholm L. Methadone for cancer-related neuropathic pain: a review of the literature. Journal of Opioid Management. 2006: 2(5): 269-76.

Medicines and Healthcare Products Regulatory Agency. Fentanyl patches: serious and fatal overdose from dosing errors, accidental exposure and inappropriate use. *Drug Safety Update*. 2008; **2**(2): 2–3.

Nicholson AB. Methadone for cancer pain. *Cochrane Database of Systematic Reviews*. 2007; **(4)**:CD003971.

Portenoy RK, Thaler HT, Inturrisi CE et al The metabolite morphine-6-glucuronide contributes to the analgesia produced by morphine infusion in patients with pain and normal renal function. Clinical Pharmacology and Therapeutics 1992; 51: 422-431.

Regnard C, Pelham A. Severe respiratory depression and sedation with transdermal fentanyl: four case studies. *Palliative Medicine.*2003; **17**: 714–16.

Sarhill N. Walsh D. Nelson KA. Hydromorphone: pharmacology and clinical applications in cancer patients. Supportive Care in Cancer. 2001; 9(2): 84-96.

Further resources

A Guide to Symptom Relief in Palliative Care, 6th ed. Regnard C, Dean M. Oxford: Radcliffe Medical Press, 2010

e-lfh: e-Learning for Healthcare contains a range of online self-learning programmes, including several relating to end-of-life care (e-ecla). Registration is required but is free. http://www.e-lfh.org.uk/projects/e-elca/index.html

PCF4- Palliative Care Formulary, 4th ed. Twycross RG, Wilcock A. www.palliativebooks.com

Twycross RG. (1999) *Morphine and the Relief of Cancer Pain: information for patients, families and friends*. Beaconsfield: Beaconsfield Publishers.

Oxford Textbook of Palliative Medicine 4th ed. Hanks G, Cherny NI, Christakis NA, Fallon M, Kaasa S, Portenoy RK. eds. Oxford : Oxford University Press, 2010.

Symptom Management in Advanced Cancer, 3rd4th edition. Twycross RG, Wilcock A, Stark-Toller C. Oxford: Radcliffe Press, 2009

Wall and Melzack's Textbook of pain, 5th ed. McMahon SB, Koltzenburg M, eds. Edinburgh : Elsevier Churchill Livingstone, 2005.

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Current Learning in Palliative care

An accessible learning programme for health care professionals

15 minute worksheets are available on:

- An introduction to palliative care
- Helping the patient with pain
- Helping the patient with symptoms other than pain
- Moving the ill patient
- Psychological and spiritual needs
- Helping patients with reduced hydration and nutrition
- Procedures in palliative care
- Planning care in advance
- Understanding and helping the person with learning disabilities
- The last hours and days
- Bereavement

Available online on

www.clip.org.uk