Analgesia in Malignant Disease (Patients not Receiving Palliative Care)

Reference:	CG1463
Written by:	Dr Daniel Yeomanson
Peer reviewer	Dr Jeanette Payne
Approved by RRGM:	11th May 2022
Approved by D&TC:	26th November 2021
Review Due:	May 2025

Intended Audience

This document contains information and clinical guidelines for management of children attending the Oncology and Haematology department. It is to be used by staff within the Trust whenever they are caring for these children either in hospital or at home.

Purpose

To guide staff in initiation and titration of opioid analgesia in patients with a malignant diagnosis. Also contains information about opioid switching and analgesia for neuropathic pain. See separate guidelines for prescribing in palliative care and at end of life.

Table of contents

1. Introduction

Many patients with malignancy experience pain, either as a direct result of their condition, following diagnostic or therapeutic interventions or due to side of effects of treatment e.g. mucositis after chemotherapy or radiotherapy.

Effective analgesia is therefore important in reducing the negative impact of a malignant diagnosis on a patient's quality of life, which in turn may improve compliance with treatment and have knock on benefits for the whole family.

These guidelines are intended to outline an approach to cancer patients with moderate to severe pain. Where relevant, reference will be made to related guidelines available on the Intranet. Specific advice for patients receiving palliative care can be found in the End of Life Care Pathway or Palliative Care Guidelines.

2. Background

The principles of effective analgesia for patients with malignancy are no different than for other children. In general, analgesia is most effective if prescribed regularly, and the oral (or nasogastric) route is usually preferred in the first instance. It is important to consider the need for breakthrough analgesia (PRN doses) to deal with painful episodes that occur between regular doses. It is helpful to ask patients to "score" their pain regularly to ensure that analgesic prescriptions are appropriate, and to remember that requirements may change as disease responds to treatment, or progresses. Information regarding useful pain assessment tools is available on the Intranet – CG712 - Pain Assessment

Although the principles are the same, there are a number of differences in the choice of analgesic agents used for patients with malignant diagnoses and they are more likely to require opioid analgesia than other patient groups. Primarily this is due to the antipyretic effects of otherwise useful analgesics such as paracetamol and ibuprofen (which may mask fever), and the difficulties of using NSAID's in patients who are at risk of thrombocytopenia. Rectal administration of analgesia (and other medication) should be avoided in neutropenic patients.

3. Mild to Moderate Pain

Although Paracetamol and NSAID's remain useful in certain situations, particularly for inpatients recovering from surgical procedures, they are not usually used as first line analgesic agents for the reasons outlined above. Due to concerns regarding Codeine use in children, and variability of Dihydrocodeine metabolism, oral morphine solution is the first choice analgesic agent.

Standard dosing (as per BNFc) is used. For mild pain, doses at the lower end of the starting dose range should be used initially, and can be titrated upwards as required (see below).. Guidance is also available on the Intranet – CG713 – Analgesia – Suggested Doses for Inpatients

4. Severe Pain

Morphine is the analgesic of choice, and may be given enterally, intravenously or (occasionally) subcutaneously. **Intramuscular administration should be avoided** as it is painful, absorption is less predictable and there are risks associated with thrombocytopenia and clotting abnormality.

Morphine doses suggested below are appropriate **starting doses** and may need to be increased if ineffective. There is no pre-defined upper limit for opiate doses, providing the pain is responsive to the opiate prescribed and the patient is not suffering unacceptable side effects (see below). Respiratory depression is the most feared side effect of opiate therapy; this must be monitored for, but rarely occurs before analgesia has been achieved.

If you are in anyway unsure about the appropriate starting dose of opiate medication, or how to adjust doses to a patient's requirements you must discuss with a consultant or oncology pharmacist before writing the prescription.

Oral Morphine

Like other analgesics, morphine works best given regularly (4 hourly). Always calculate the total daily dose, and prescribe a PRN breakthrough dose of 10% the total daily amount.

Suggested initial **ORAL** starting doses as per BNFc

Age	**Initial dose in Opioid naïve patients**
Child 1 – 2 months	50 – 100 micrograms/kg 4 hourly
Child 3 – 5 months	100 – 150 micrograms/kg 4 hourly
Child 6 – 11 months	200 micrograms/kg 4 hourly
Child 1 years	200 – 300 micrograms/kg 4 hourly
Child 2-11 years	200 – 300 micrograms/kg 4 hourly Max dose 10mg
Child 12 – 17 years	5 – 10 mg 4 hourly

Adapted from BNFc (App, 22/7/21)

Approximate Dose Equivalence – Oral Weak Opioids to Oral Morphine

Drugs	Ratio	Calculation	Example
Dihydrocodeine to Morphine	10:1	Divide 24h Dihydrocodeine dose by 10	Dihydrocodeine 240mg/24h PO → Morphine 24mg/24h PO
Tramadol to Morphine	10:1	Divide 24h Tramadol dose by 10	Tramadol 400mg/24h PO → Morphine 40mg/24h PO

Adapted from BNFC (app, 22/7/21)

Once a child is stable on regular oral morphine, it is often possible to switch them to a modified release preparation, such as MST. This is given twelve hourly, splitting the previous total daily dose (including any PRN doses for given for breakthrough) between the two doses. Again remember to prescribe a PRN dose for breakthrough (10% the total daily dose).

Patients on MST should be reviewed every 48-72 hours and the dosage adjusted if more than 1 dose of breakthrough medication is needed each day. In this situation, the total daily dose of MST should be increased to include the amount given each day as PRN doses. A new breakthrough dose should also be prescribed to ensure that it remains at 10% of the total daily dose.

Intravenous Morphine

Intravenous morphine may be needed for patients with acute severe pain requiring immediate analgesia, or for those in whom the enteral route is unsuitable e.g. post op, severe mucositis etc… This may be given as a continuous infusion, or via Nurse Controlled (NCA) or Patient Controlled Analgesia (PCA). NCA and PCA are only available via the Pain Team.

Patients starting directly on an intravenous morphine infusion are usually given an intravenous loading dose, followed by infusion which can be titrated upward as needed. Titrations should be carried out every 6 hours, in increments of 10 – 20% each time. Careful monitoring of respiratory rate and other side effects are required during the titration phase.

Suggested starting doses for Opiate naïve patients as per BNFc (via App 21/7/21). Doses should be titrated to effect, and given over at least 5 minutes.

Age	IV PRN or Loading Dose	Initial rate for Infusion
Neonate	50 micrograms/kg (6 hourly for PRN)	5 – 20 micrograms/kg/hr
1 – 5 months	100 micrograms/kg (6 hourly for PRN)	10 – 30 micrograms/kg/hr
6 months – 11 years	100 micrograms/kg (4 hourly for PRN)	20 – 30 micrograms/kg/hr
12 – 17 years	5 mg (4 hourly for PRN)	20 – 30 micrograms/kg/hr

Infusions should be made up as follows. The loading dose can be omitted if converting from oral analgesia, providing pain relief is adequate e.g. changing due to unavailability of oral route

Patients < 50 kg Prescribe Morphine 1mg/kg in 50mls of 0.9% Sodium Chloride
1ml/hr = 20 micrograms/kg/hr

e.g. 35 kg child
Prescribe 35mg in 50ml 0.9% Sodium Chloride
Dose per ml = 35mg divided by 50mls = 0.7mg/ml = 700 micrograms/ml
Dose per kg in 1 ml = 700 microgram/ml divided by 35kg = 20microgram/kg/ml
so 1ml/hr gives 20 micrograms/kg/hr

Patients >50kg Write up Morphine 50mg in 50mls 0.9% Sodium Chloride = 1000 microgram/ml
Document dose (microgram/kg/hr) delivered at rate of 1ml/hr on prescription

e.g. 70 kg child
Calculate morphine concentration in microgram/kg/ml
= Drug concentration divided by weight
= 1000 microgram/ml divided by 70 kg = 14 microgram/kg/ml
Therefore dose per kg in 1ml = 14 micrograms/kg

Prescribe dose range in mcg/kg/hr and rate in mls/hr
Range = 20 – 60 microgram/kg/hr
Rate = Dose (microgram/kg/hr) divided by concentration (microgram/kg/ml)
Rate @ 20 microgram/kg/hr = 20 divided by 14 = 1.4 ml/hr
Rate @ 60 microgram/kg/hr = 60 divided by 14 = 4.3 ml/hr

Conversion from oral to parenteral opiates

When changing from one route to another, differences in bioavailability mean that doses must be adjusted for equivalence using the tables below.

If changing to IV analgesia because the enteral route is no longer available, ensure that the opiate dose prescribed is equivalent to the previous oral morphine dose. Consider giving a loading dose (10% of total daily dose) and adding an extra 10 – 20% to the total daily dose prescribed if the change is being made because analgesia was inadequate. Diamorphine is used preferentially in the community setting as its greater solubility allows it to be delivered in a smaller volume via a portable infusion device.

Approximate Dose Equivalence – Oral Morphine to IV/Subcutaneous Opiates

Drugs	Ratio	Calculation	Example
Oral Morphine to IV Morphine	2:1	Divide 24 hour oral morphine dose by 2	Morphine 10mg/24h PO → Morphine 5mg/24h SC/IV
Oral Morphine to IV Diamorphine	3.3:1	Divide 24 hour oral morphine dose by 3.3	Morphine 10mg/24h PO → Diamorphine 3mg/24h SC/IV

Adapted from BNFC (app, 21/7/21)

Transdermal Opiates (Fentanyl patches)

Fentanyl patches provide a good alternative to oral MST in patients who have stable analgesic requirements. They are less suitable for titration in the acute situation due to the relatively slow onset (and offset) of action. The dose conversion table (below) gives information on the appropriate strength of patch for a given total daily dose of morphine. Oral morphine should be continued for the first 12 hours after the patch is applied, and a suitable PRN dose should be available alongside the patch (either oral morphine or fentanyl lozenges). The need for ongoing PRN analgesia suggests that the patch strength needs to be increased.

Each patch works for 72 hours and therefore needs changing every 3 days. They are prescribed in micrograms/hr strengths and the lowest dose patch provides 12micrograms/hr (roughly equivalent to 30mg/day of oral morphine). Smaller doses can be delivered by occluding part of the patch with Opsite, or by cutting the patch in half (depends on patch manufacturer, check with pharmacy), but this is not 100% accurate and best avoided if possible.

Approximate Dose Equivalence – Oral Morphine to Transdermal Fentanyl

Total Daily Dose of ORAL Morphine	Approximately Equivalent Patch Strength
30 mg per day	Fentanyl 12 micrograms/hr patch
60 mg per day	Fentanyl 25 micrograms/hr patch
120 mg per day	Fentanyl 50 micrograms/hr patch
180 mg per day	Fentanyl 75 micrograms/hr patch
240 mg per day	Fentanyl 100 micrograms/hr patch

Adapted from BNFc (app, accessed 21/7/21)

5. Opiate Side Effects

Constipation is the most common opiate side effect that causes problems in paediatric practice. Always prescribe an appropriate laxative.

Nausea and Vomiting is relatively rare in children. If it occurs, cyclizine is usually effective, although symptoms may also be controlled by other antiemeitics the patient is already on. Haloperidol is an alternative, particularly for patients receiving palliative care.

Pruritis is a relatively common problem. It is probably not mediated via histamine receptors, and chlorphenamine is often of limited use. Ondansetron often helps, via effects on serotonin receptors, although there may be a cumulative effect on constipation. Opioid switching is another approach, with oxycodone often tried first.

Sedation can occur when opioids are started. This may be a direct effect of the drug, or reflect adequate analgesia which allows the child to catch up on sleep they have been missing due to pain. This effect usually wears off in a few days.

Respiratory depression rarely occurs if medication is prescribed and titrated carefully, as pain is a very effective respiratory stimulant. It can occur in inadvertent overdose, if pain suddenly improves e.g. response to chemoradiotherapy, introduction of additional effective analgesia (spinal catheter, nerve block) or following acute renal or hepatic failure. Mostly this can be managed with dose reduction; naloxone should be used with caution as it is likely to completely reverse analgesia at the doses required to treat respiratory depression.

Dependence, Tolerance and Addiction concerns may lead to a reluctance to use opiates. Physiological dependence, resulting in withdrawal phenomena, does occur and patients on higher doses of opiates should be weaned off them gradually (reduce 25% every 48hrs).

Patients who have been on high doses of opiates for a prolonged period (often whilst on ICU) may require additional interventions during weaning (see guidelines on Intranet – "PCCU Clonidine Guideline").

Tolerance also occurs, and may require dose increases or opiod rotation. If doses are escalating rapidly, progressive disease is more likely than tolerance.

Addiction, a craving for opiates, is rare and parents should be reassured that their child is not going to become an addict due to their use of opiate analgesia.

6. Neuropathic Pain

Neuropathic pain is often described as burning or tingling and can be very unpleasant. The distribution may be dermatomal. It does not respond well to opiate analgesia.

The mainstay of treatment for neuropathic pain are the tricyclic antidepressants and anticonvulsants. There is little evidence that one is better than the other (NNT = 3 for both) but due to potential side effects of tricyclics, anticonvulsants are usually preferred in paediatric practice.

Gabapentin is usually used in the first instance. Pregabalin is an alternative prodrug that can be helpful in those who do not respond to, or are intolerant of Gabapentin. Discuss the use of these drugs with a consultant. Starting doses are as per BNFc.

Both Ketamine and Methadone have a potential role in the treatment of severe neuropathic pain – discuss with Pain Team.

7. Other analgesic options

Some patients may experience particularly troublesome side effects with certain opiates and there is some evidence that these can be alleviated by switching to a different drug within the class. This decision should usually be made by a consultant, often in conjunction with the Pain Team, who should be contacted as soon as opiate intolerance is suspected. The pain team should also be involved early with patients whose pain control is inadequate with a simple opiate infusion and who may benefit from NCA or PCA. .

Others may have pain that is unresponsive to simple opiates. They may benefit from a change to Methadone (broad range of receptors targeted) or Ketamine (NDMA receptors). The conversion to, or initiation of these drugs is complex and should only be done in conjunction with the Pain Team.

In selected cases other interventions such as TENS, acupuncture, visualisation, relaxation and physiotherapy may help with pain management. More complex pain may require a range of additional techniques including regional blocks, intrathecal analgesia or in extreme circumstances, neurolysis. The Pain Team will be closely involved with such patients.

8. Other Resources

Oxford Textbook of Palliative Care for Children (Library, Dr Yeomanson's Office)

Sheffield Childrens Hospital Pain Management Service
Specialist Nurse - Bleep 139 (Monday – Friday 0830 – 1700)
On Call Anaesthetist – Bleep 525 at all other times

Intranet

Sheffield Children's NHS Foundation Trust (2021) Pain Management Guideline. Pain Assessment. SCH Guideline (CG712)

Sheffield Children's NHS Foundation Trust (2021) Analgesia – Analgesia Suggested Drug Doses for Inpatients. SCH Guideline (CG713)

Internet

Basic Symptom Control in Paediatric Palliative Care 4th Edition, 2017
https://www.togetherforshortlives.org.uk/wp-content/uploads/2017/12/ProRes-Symptom-Control-Manual-with-4th-edition-formulary-2017.pdf [accessed 22/7/21]

APPM Master Formulary appm.org.uk [accessed 21/7/21]

9. References

Oxford Textbook of Palliative Care for Children. Goldman, Liben and Hain. (1st Edition, 2006) Oxford University Press

Paediatric Formulary Committee. BNF for Children (app) London: BMJ Group, Pharmaceutical Press, and RCPCH Publications (via app, 22/7/21)

www.palliativedrugs.com accessed 22/7/21 (requires subscription)

Jassal S. Basic Symptom Control in Paediatric Palliative Care [Internet]. 4th ed. Together for short lives and The Rainbows Hospice for Children and Young Adults; 2017 [cited 2022 Apr 29]. Available from: www.togetherforshortlives.org.uk/app/uploads/2017/12/ProRes-Symptom-Control-Manual-with-5th-edition-formulary-2020.pdf

APPM Master Formulary [Internet]. [cited 2022 Apr 29]. Available from: https://www.appm.org.uk/_webedit/uploaded-files/All%20Files/Event%20Resources/2020%20APPM%20Master%20Formulary%202020%20protected.pdf