Converting oral to intravenous or subcutaneous infusions

- Why change to an alternative route?
- Differences in routes
- Pharmacokinetics
- Converting to intravenous or subcutaneous infusions
- Opiate conversion tables
- Palliative care drug boxes
- Palliative care dose calculator
- Questions and discussion
Why change to an alternative route?

- WHO guidelines
  - By the most appropriate route
- Alternatives
  - Enteral
  - Buccal
  - Rectal
  - Transdermal
  - Subcutaneous
  - Intravenous
  - Spinal
- Indications
  - Nausea, vomiting
  - Poor absorption
  - Difficulties with intake
    - Large number of drugs
  - Rapidly escalating symptoms requiring dose titration
## Enteral route

<table>
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<tr>
<th>Oral</th>
<th>Jejunostomy</th>
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<tr>
<td>• Most physiological</td>
<td>• By-pass smell and taste</td>
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<td>• First pass metabolism</td>
<td>• initiation of gastrointestinal tract mechanisms</td>
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<tr>
<td></td>
<td>• By-pass mastication</td>
</tr>
<tr>
<td><strong>Gastrostomy</strong></td>
<td>• By-pass salivary amylase</td>
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<tr>
<td>• By-pass smell and taste</td>
<td>• By-pass stomach acid</td>
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<tr>
<td>• By-pass mastication</td>
<td>• Less able to tolerate large volume boluses</td>
</tr>
<tr>
<td>• By-pass salivary amylase</td>
<td>• Finer bore tube</td>
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<tr>
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</table>

**Jejunostomy**

- By-pass smell and taste initiation of gastrointestinal tract mechanisms
- By-pass mastication
- By-pass salivary amylase
- By-pass stomach acid
- Less able to tolerate large volume boluses
- Finer bore tube
Intravenous route

- By pass first pass metabolism
- Rapid onset of action
- Tolerate rapid infusion of large volumes
- Tolerate higher or lower pH
- Tolerate irritant substances
  - Requirement for central venous access
Subcutaneous route

- Bolus or infusion into subcutaneous tissues
- Absorption mainly via lymphatics
- Slower onset of action than intravenous
- Slower maximum bolus size and rates of infusion

Common misconceptions
- 4th step on WHO ladder
- Superior analgesia
- Impending death
Siting a subcutaneous line

- Chest
- Abdomen
- Thigh
- Upper arm

Avoid sites that are
- Infected
- Oedematous
- Previously irradiated
- Near or over tumour site
- Skin folds
- Breast tissue
- Near or over joints
Infusion site problems

- Allergy to nickel in needles
- Chemical reaction from drugs
- Glass particles from ampoule
- Infection
- pH < 2 or >11
- Sterile abscess
- Hypertonic solution
- Hypotonic solution
- Drugs
  - Cyclizine
  - Levomepromazine
  - Higher doses of diamorphine

- Reduce risk by
- Plastic infusion device
- 0.9% saline as a diluent except
- Water for injection as a diluent for
  - Cyclizine
  - Diamorphine >40mg/ml
Which drugs can be given subcutaneously?

- Many drugs may be suitable but evidence and clinical experience is lacking.
- Most drugs given subcutaneously have a product licence.
- Licence does not usually extend to:
  - Subcutaneous administration
  - Palliative care indications
  - Children or babies

- Drugs that cannot be given subcutaneously:
  - pH < 2
  - pH > 11

- Certain excipients:
  - Preservatives e.g. sodium benzoate
  - Solubilizing agents e.g. polyethylene glycol, ethanol, propylene glycol, glycerin

Association for Paediatric Palliative Medicine
Mixing drugs in a syringe driver

- Over 2000 possible combinations
- Salts precipitating
- New compound formed
  - Reduced efficacy
  - Toxicity
- Precipitate may not be visible or may form and re-dissolve
- Gold standard is laboratory testing
- Acceptable if
  - Solution is clear
  - Demonstrable efficacy

- Combination of acidic and alkaline drugs most likely to precipitate
- Most drugs are acidic
  - Give alkaline drugs separately
- Alkaline drugs
  - Dexamethasone
  - Diclofenac
  - Furosemide
  - Ketorolac
  - Phenobarbital
Mixing drugs in a syringe driver

- Medicines Act 1968 requires a licence for manufacturing drugs
- 2009 Medicines Act interpreted by MHRA as including mixing drugs prior to administration
- Commission on Human Medicines advised MHRA
  - Mixing drugs is acceptable when clinically appropriate and essential
  - Research is needed
  - No prosecutions while legislation is under review
Managing a continuous infusion

- Avoid direct exposure to sunlight
  - Especially levomepromazine
- Maintain at room temperature
  - Not under bedclothes
- Change infusion every 24 hours
  - Microbiology
  - Stability issues
- Calculate the rate first then prime the line
- Infusion will run through early
- Patient will not receive full dose if infusion rate is calculated after priming the line
- Increasing volume of infusion reduces the impact either way

Actual duration of infusion = Volume of giving set x 24 hours / Volume of infusion
Pharmacokinetics

- **Bioavailability**
  - Fraction of unchanged drug reaching systemic circulation

- **Half-life**
  - Time required to halve the amount of drug in the body

- **Onset of action**
  - Time between administration of drug to onset of desired action

- **Duration of action**
  - Time between onset of action and cessation of desired action
Infusion kinetics

Steady State
- Attained after approximately four half-times
- Time to steady state independent of dosage

Steady State Concentrations

TIME (multiples of elimination half-time)

CONCENTRATION
Properties of common drugs used in palliative care

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bio-availability</th>
<th>Plasma half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>35% oral</td>
<td>1.5 hours</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>N/A</td>
<td>3 minutes (metabolized to active metabolites)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>75% buccal</td>
<td>2 – 5 hours (up to 10 hours in CSI)</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>20 – 40% oral</td>
<td>15 – 30 hours</td>
</tr>
<tr>
<td>Cyclizine</td>
<td>[100%] No data</td>
<td>20 hours</td>
</tr>
<tr>
<td>Hyoscine hydrobromide</td>
<td>60 – 80% sublingual</td>
<td>5 – 6 hours</td>
</tr>
</tbody>
</table>
Available guidance

- APPM Master formulary
- BNF for children
- www.Palliativedrugs.com
- Palliative Care Formulary
- Use the guidance?
- Use first principles?
Converting oral to intravenous or subcutaneous infusions

- Review all medication
  - Stop unnecessary medication
  - Change to alternative routes where possible
  - Continue essential medication with no alternative routes
- Consider converting anti-emetics to intravenous or subcutaneous route first
- Dose of intravenous (or subcutaneous) drug administered over 24 hours
  \[ \text{Dose} = \text{total oral dose over 24 hours} \times \text{bioavailability} \]
Worked example: Jamie, cystic fibrosis

Before
- Dornase alpha, 2.5mg, neb, BD
- Midazolam 5mg, PEG, BD, plus PRN
- Morphine oral solution, 5mg PEG, QDS plus PRN
- Nystatin, 500,000U, PO, QDS
- Pancreatin, 8 capsules, PO, with meals
- Paracetamol, 425mg, PEG, PRN max QDS
- Prednisolone, 25mg, PEG, OD
- Gaviscon, 10ml, PEG, QDS
- Sodium chloride, 50mmol, PEG, BD
- Sodium chloride 7%, 4ml Neb PRN
- Sodium valproate, 380mg, PEG, BD

After
- Dornase alpha, 2.5mg, neb, BD
- Midazolam 2mg, IV/SC, PRN max hourly
  = 0.4 (oral bioavailability) x 5mg
- Midazolam infusion 6mg/24 hours IV
  = 0.4 x 15mg (total dose in last 24h)
- Morphine infusion 15mg/24 hours IV
  = 0.5 (oral bioavailability) x 30mg (total dose in last 24h)
- Morphine bolus 2.5mg IV/SC
  PRN max hourly = 1/6 of infusion
- Sodium chloride 7%, 4ml Neb PRN
- Sodium valproate, 380mg, PEG, BD
Palliative care drug boxes

- Method for ensuring prompt and effective symptom management and avoiding unnecessary hospital admission during end of life care at home
- Contain necessary medication for symptom management pre-prescribed to be administered via continuous intravenous or subcutaneous infusion
- Prescribed a few days before they are expected to be needed
- Remain in the home until after the patient has died.
Alder Hey Specialist Palliative Care team: Palliative care drug boxes

- Introduced in 1998.
- Use of the palliative care drug boxes and supporting documentation reviewed after 24 boxes had been used and minor modifications made.
- Further retrospective review of all palliative care drug box prescriptions and medication use during the period July 2001 to June 2007.
Alder Hey Specialist Palliative Care team: Palliative care drug boxes

- Eighty boxes prescribed for 75 children
  - 55 with cancer and 20 with other life limiting conditions
  - 34 intravenous and 40 subcutaneous
- Two children each had 3 box prescriptions at different times
- Twenty one palliative care drug box prescriptions were not used
  - 8 oncology
  - 13 non oncology
Eighty infusions commenced

Most common combinations were:
  - Diamorphine, midazolam & leveomepromazine (N=13)
  - Diamorphine, midazolam & cyclizine (N=11)
  - Diamorphine & cyclizine (N=9).

Contents of the syringe were
  - Renewed every 24 hours
  - Continued for a median of 75 hours (inter-quartile range 17 - 256 hours).
Seventy eight percent of symptoms were controlled with a combination of one or more of the following:

- A strong opiate, (morphine or diamorphine)
- Cyclizine
- Haloperidol
- Levomepromazine
- Midazolam
- Hyoscine hydrobromide

Where medication other than these 6 “essential drugs” was required to control symptoms this had usually been started before end of life care.
Drug boxes remained in the house a median of 4 days (range <1 to 106 days).

Despite several families with known substance abusers all medication was accounted for except 1 instance when the morphine “disappeared” from the unused box after the child’s death.
Opiate conversion tables

<table>
<thead>
<tr>
<th>Weight</th>
<th>Morphine 4 hourly</th>
<th>MST b.d.</th>
<th>Morphine IV or s.c. 4 hourly</th>
<th>Morphine IV or s.c. 24 hours</th>
<th>Oxycodone 4- 6 hourly</th>
<th>Oxycodone IV</th>
<th>Diamorphine</th>
<th>Diamorphine IV</th>
<th>Fentanyl 72 Hourly</th>
<th>Fentanyl iv 24 hours IV or s.c.</th>
<th>Alfentanil iv 24 hours IV or s.c.</th>
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<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>Oral</td>
<td>IV or s.c. 4 hourly</td>
<td>IV or s.c. 24 hours</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
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</table>

Opiate equivalents: equivalent dose of external morphine = dose of opiates x potency ratio

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<th>Approximate potency ratios</th>
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<th>2</th>
<th>3</th>
<th>100</th>
<th>30</th>
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<td>2</td>
<td>2</td>
<td>3</td>
<td>100</td>
<td>30</td>
</tr>
</tbody>
</table>
| Equivalent dose of fentanyl patch: Equivalent dose of 4-6 hourly morphine = patch strength (micrograms) x 0.6.

Notes: Starting doses are given as per Alder Hey Specialist Palliative Care team guidelines. Using opiates equivalents to calculate starting doses of opiates other than morphine may give a higher dose than if calculated from reference doses per kg. Therefore the lowest doses have been given for safety reasons.
# Palliative care drug box dose calculator

<table>
<thead>
<tr>
<th>Name</th>
<th>Jo Bloggs</th>
<th>NHS no</th>
<th>123 456 7890</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of birth</td>
<td>10-May-06</td>
<td>Age</td>
<td>10.081 years</td>
</tr>
<tr>
<td>Date</td>
<td>08-Jun-16</td>
<td>Weight</td>
<td>29 kg</td>
</tr>
</tbody>
</table>

## 24 hour infusions via syringe driver

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Indications</th>
<th>Recommended dose mg/kg/24hrs</th>
<th>Actual dose range mg/24hrs; round to 2 digits to administer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclizine*</td>
<td>SC or IV</td>
<td>Nausea and vomiting</td>
<td>1.5</td>
<td>43.5 87 44 87</td>
</tr>
<tr>
<td>Dexamethasone*</td>
<td>SC or IV</td>
<td>Raised intracranial pressure, nausea and vomiting</td>
<td>6</td>
<td>12 6 12</td>
</tr>
<tr>
<td>Diamorphine*$</td>
<td>SC or IV</td>
<td>Pain</td>
<td>0.3</td>
<td>8.7 8.7 8.7 19.575</td>
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<tr>
<td>Haloperidol*</td>
<td>SC or IV</td>
<td>Agitation, nausea and vomiting</td>
<td>0.025</td>
<td>0.725 2.465 0.725 2.465</td>
</tr>
<tr>
<td>Hyoscine hydrobromide*</td>
<td>SC or IV</td>
<td>Excess oral secretions</td>
<td>0.03</td>
<td>0.87 1.74 0.87 1.74</td>
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<tr>
<td>Levomepromazine</td>
<td>SC or IV</td>
<td>Antiemetic</td>
<td>0.1</td>
<td>2.9 11.6 2.9 11.6</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>SC or IV</td>
<td>Sedative antipsychotic</td>
<td>0.35</td>
<td>10.15 87 10.15 87</td>
</tr>
<tr>
<td>Metoclopramide*</td>
<td>SC or IV</td>
<td>Antiemetic</td>
<td>0.3</td>
<td>8.7 14.5 8.7 14.5</td>
</tr>
<tr>
<td>Midazolam*</td>
<td>SC or IV</td>
<td>Sedative antipsychotic</td>
<td>0.24</td>
<td>6.96 12.18 7 15.75</td>
</tr>
<tr>
<td>Midazolam*</td>
<td>SC or IV</td>
<td>Seizures</td>
<td>1.2</td>
<td>34.8 100 35 78.75</td>
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<tr>
<td>Morphine*$</td>
<td>SC or IV</td>
<td>Pain</td>
<td>0.4</td>
<td>11.6 26.1 12 27</td>
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</tbody>
</table>

## Bolus doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Indications</th>
<th>Recommended dose (mg/kg)</th>
<th>Actual dose (mg)</th>
<th>Dose as 1/6 of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorphenamine</td>
<td>IV</td>
<td>Anaphylaxis</td>
<td>0.1</td>
<td>2.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Cyclizine</td>
<td>SC or IV</td>
<td>Nausea and vomiting</td>
<td>0.5</td>
<td>14.5</td>
<td>0</td>
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<tr>
<td>Diamorphine*</td>
<td>SC or IV</td>
<td>Pain</td>
<td>0.075</td>
<td>2.175</td>
<td>2.9 1.45 3.2625</td>
</tr>
<tr>
<td>Diazepam</td>
<td>PR</td>
<td>Agitation, convulsions</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>IV</td>
<td>Anaphylaxis</td>
<td>2</td>
<td>58</td>
<td>116</td>
</tr>
<tr>
<td>Hyoscine hydrobromide*</td>
<td>SC or IV</td>
<td>Respiratory tract secretions</td>
<td>0.01</td>
<td>0.29</td>
<td>0.29</td>
</tr>
<tr>
<td>Midazolam</td>
<td>SC or IV</td>
<td>Anxiety or agitation</td>
<td>0.06</td>
<td>1.74</td>
<td>2.9 2 4.5</td>
</tr>
<tr>
<td>Midazolam</td>
<td>SL</td>
<td>Anxiety or agitation</td>
<td>0.07</td>
<td>2.03</td>
<td>10</td>
</tr>
<tr>
<td>Midazolam</td>
<td>SL</td>
<td>Seizures</td>
<td>0.3</td>
<td>8.7</td>
<td>10</td>
</tr>
<tr>
<td>Morphine*$</td>
<td>SC or IV</td>
<td>Pain</td>
<td>0.1</td>
<td>2.9</td>
<td>4.35 0 0</td>
</tr>
</tbody>
</table>
Personal practice points

- **Breakthrough doses**
  - 1/6 for oncology patients
  - 1/6 - 1/10 for non oncology patients
  - ? Rescue doses for midazolam

- **Dose ranges**
  - Starting dose – 2.25 x starting dose
  - Allows for 2 x 50% increases then review

- **If in doubt start at the lower dose**

- **Midazolam doses**
  - Lower doses than APPM master formulary
  - Extrapolated from adult doses (PCF)

- **Round doses down to two digits**
Summary

- If enteral medication is not tolerated or effective, alternative routes of administration are required. Conversion to intravenous or subcutaneous infusions is not always necessary or possible.
- It takes time for an infusion to reach steady state.
- Converting to intravenous or subcutaneous infusions should be undertaken as part of an overall medication review.
- Opiate conversion tables and a palliative care dose calculator increase safety and reduce time taken when converting to intravenous or subcutaneous infusions.
Questions and discussion

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