Converting oral to intravenous or subcutaneous infusions

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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

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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

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Enteral route

Oral

- Most physiological
- First pass metabolism

Gastrostomy

- By-pass smell and taste initiation of gastrointestinal tract mechanisms
- By-pass mastication
- By-pass salivary amylase

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

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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

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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

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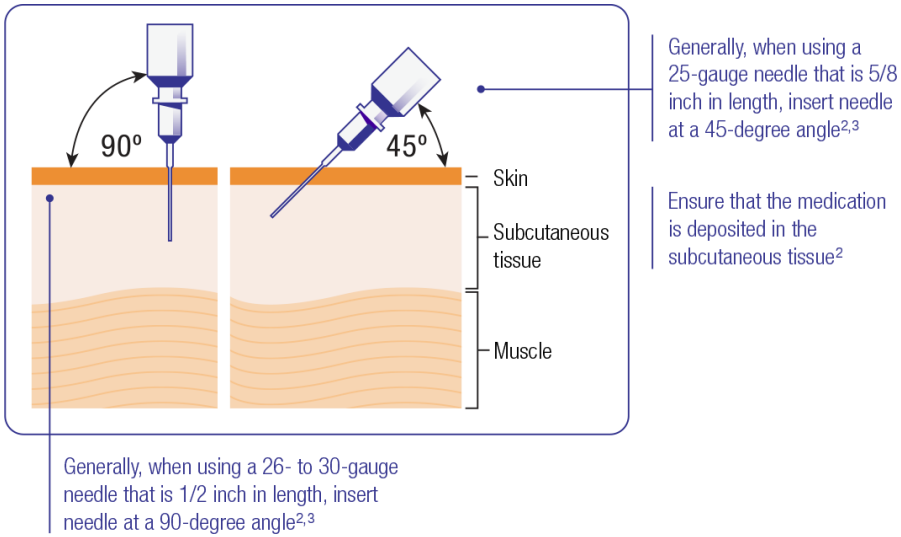
Siting a subcutaneous line

- 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

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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

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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. polyethelene glycol, ethanol, propylene glycol, glycerin

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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

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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

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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

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

- 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

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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

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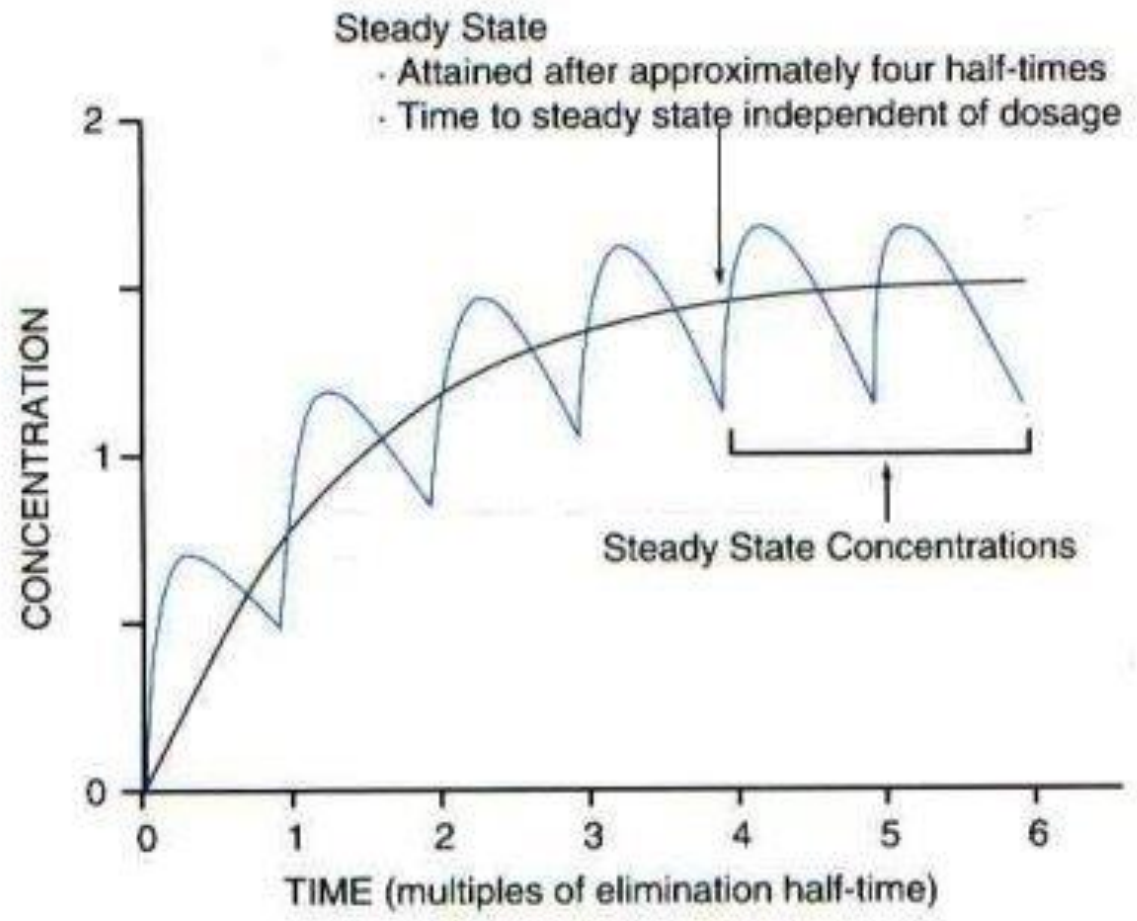
Infusion kinetics



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Properties of common drugs used in palliative care

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

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Available guidance

- APPM Master formulary
- BNF for children
- www.Palliativedrugs.com
- Palliative Care Formulary
- Use the guidance?
- Use first principles?

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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

  = total oral dose over 24 hours x bioavailability

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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

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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.

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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.

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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

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Alder Hey Specialist Palliative Care team: Palliative care drug boxes

- 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).

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Alder Hey Specialist Palliative Care team: Palliative care drug boxes

- 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.

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Alder Hey Specialist Palliative Care team: Palliative care drug boxes

- 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.

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Opiate conversion tables

Weight	Morphine 4 hourly	MST b.d.	Morphine	Morphine	Oxynorm# 4 - 6 hourly	Oxycontin# b.d	Diamorphine	Diamorphine	Fentanyl 72 Hourly	Fentanil iv	Alfentanil iv
	Oral	Oral	IV or s/c 4-6 hourly	IV or s/c 24 hours	Oral	Oral	4 hourly IV or s/c	24 hours IV or s/c	Transdermal	24 hours IV or s/c	24 hours IV or s/c
	10mg/5ml; 30mg/5ml;	Granules 20, 30, 60, 100	10, 15, 20 & 30mg/ml x 1ml & 2ml		liquid 5mg/5ml, 10mg/ml	tablets 5,10, 20,	ampoules; 5, 10,	ampoules; 5, 10,	patches 12, 25,	50microgram/ml	500microgram/ml
	100mg/5ml	200mg/sachet			capsules; 5, 10, 20mg	40, 80mg	30, 100, 500mg	30, 100, 500mg	50, 75, 100microgram/hr	x 2ml or 10ml	x 2ml or 10ml
	tablets (scored); 10, 20, 50mg	tablets 5, 10, 15, 30, 60									5mg/ml x 1ml
		100, 200mg			# = Oxycodone not licenced in UK under 18 years						
(starting dose only)	<3months 50 - 100 microgram/kg/dose		<3 months 25 - 50 microgram/kg/dose			<3 month 20microgram/kg/dose					
	3 - 6 month 100 - 150 microgram/kg/dose		3 - 6 months 50-75 microgram/kg/dose			3 - 6 months 25 - 50 microgram/kg/dose					
	6 - 12 months 200 microgram/kg/dose		6 - 12 months 100 microgram/kg/dose			6 -12 months 75 microgram/kg dose					
	>1 year 200 - 300microgram/kg/dose		>1 year 100 - 150 microgram/kg/dose		100 - 150 microgram/kg/dose WHO	75 - 100 microgram/kg/dose					
3	0.25	0.75	0.125	0.5	0.10		0.05	0.3		0.015	0.03
5	0.5	1.5	0.25	1.5	0.25		0.2	1		0.03	0.1
7	1.5	4.5	0.75	4.5	0.75		0.5	3		0.09	0.3
10	2	6	1	6	1		0.8	5	6	0.12	0.5
12	3	9	1.5	9	2		1	6	6	0.18	0.6
15	4	12	2	12	3		1.5	8	12	0.24	0.75
20	5	15	2.5	15	3		2	10	12	0.3	1
25	7.5	20	3.5	20	4	10	2	10	12	0.4	1.25
30	7.5	20	3.5	20	4	10	2.5	15	12	0.4	1.5
35	10	30	5	30	5	10	2.5	15	25	0.6	1.75
40	10	30	5	30	5	10	3.5	20	25	0.6	2
45	10	30	5	30	5	10	3.5	20	25	0.6	2.25
50	10	30	5	30	5	10	4.5	25	25	0.6	2.5
Over 50kg and adult	15	45	7.5	45	5	10	5	30	37	0.9	3
Approximate	20	60	10	60	10	30	6	40	50	1.2	4
conversion	25	75	12.5	75	15	30	8	50	62	1.5	5
	30	90	15	90	15	40	10	60	75	1.8	6
	40	120	20	120	20	60	15	80	100	2.4	8
	50	150	25	150	25	80	15	100	125	3	10
	70	210	35	210	30	100	20	140	175	4.2	14
	90	270	45	270	40	120	30	180	225	5.4	18
	110	330	55	330	50	160	40	220	275	6.6	22
	140	420	70	420	70	200	50	280	350	8.4	28
	170	510	85	510	80	240	60	340	425	10.2	34
Opiate equivalents:	equivalent dose of enteral morphine = dose of opiate x potency ratio					equivalent dose of other opiate = dose of enteral morphine/ potency ratio					
Approximate potency ratios	1		2		2		3			100	30
Fentanyl patch	Equivalent dose of 4 - 6 hourly morphine = patch strength (microgram/hr) x 0.6										

Notes: Starting doses are given as per Alder Hey Specialist Palliative Care team guidelines. Using opiate 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.

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Palliative care drug box dose calculator

Name	Jo Bloggs		NHS no	123 456 7890				
Date of birth	10-May-06		Age	10.081	years			
Date	08-Jun-16		Weight	29	kg			
24 hour infusions via syringe driver								
Drug	Route	Indications	Recommended dose				Actual dose range	
			mg/kg/24hrs		mg/24hrs		mg/24hrs; round to	
							2 digits to administer	
			From	To	From	To	From	To
Cyclizine*	SC or IV	Nausea and vomiting	1.5	3	43.5	87	44	87
Dexamethasone*	SC or IV	Raised intracranial pressure, nausea and vomiting			6	12	6	12
Diamorphine*$	SC or IV	Pain	0.3	0.3	8.7	8.7	8.7	19.575
Haloperidol*	SC or IV	Agitation, nausea and vomiting	0.025	0.085	0.725	2.465	0.725	2.465
Hyoscine hydrobromide*	SC or IV	Excess oral secretions	0.03	0.06	0.87	1.74	0.87	1.74
Levomepromazine	SC or IV	Antiemetic	0.1	0.4	2.9	11.6	2.9	11.6
Levomepromazine	SC or IV	Sedative antipsychotic	0.35	3	10.15	87	10.15	87
Metoclopramide*	SC or IV	Antiemetic	0.3	0.5	8.7	14.5	8.7	14.5
Midazolam*	SC or IV	Anxiolytic sedative	0.24	0.42	6.96	12.18	7	15.75
Midazolam*	SC or IV	Seizures	1.2	7.2	34.8	100	35	78.75
Morphine*$	SC or IV	Pain	0.4	0.9	11.6	26.1	12	27
Bolus doses								
Drug	Route	Indications	Recommended dose (mg/kg)		Actual dose (mg)		Dose as 1/6 of infusion	
			From	To	From	To		
Chlorphenamine	IV	Anaphylaxis	0.1	0.2	2.9	5.8		
Cyclizine	SC or IV	Nausea and vomiting	0.5	1	14.5	0		
Diamorphine$	SC or IV	Pain	0.075	0.1	2.175	2.9	1.45	3.2625
Diazepam	PR	Agitation, convulsions				10		
Hydrocortisone	IV	Anaphylaxis	2	4	58	116		
Hyoscine hydrobromide	SC or IV	Respiratory tract secretions	0.01	0.01	0.29	0.29		
Midazolam	SC or IV	Anxiety or agitation	0.06	0.1	1.74	2.9	2	4.5
Midazolam	SL	Anxiety or agitation	0.07	0.12	2.03	10		
Midazolam	SL	Seizures	0.3		8.7	10		
Morphine$	SC or IV	Pain	0.1	0.15	2.9	4.35	0	0

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

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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

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Questions and discussion

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