Alternative Routes of Drug Administration (analgesia)

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Alternative Routes of Drug Administration

• Introduction
• Subcutaneous Route
  – Contemporary Issues
  – Compatibility
• Future Options
Classification

Enteral
- Oral
- Sublingual
- Buccal
- Rectal

Parenteral
- Inhalation
- Injection
- Transdermal
- Intravenous
- Intramuscular
- Subcutaneous
- Intrathecal

Topical
- Skin
- Intranasal
- Ocular
- Mucosal – throat, ear, mouth

May have local and/or systemic effects
Choice of Route

- Condition of the patient
  - unconscious, vomiting
- Available formulations
- Physical & chemical properties of drug
  - solid/liquid/gas; solubility; stability; pH
- Rapidity of response
- Site of desired action
  - E.g. localised or generalised; approachable?
Choice of Route

- When oral route no longer available:
  - Buccal/SL
  - PR
  - Transdermal
  - Intranasal
  - IV
  - IM
  - SC
POSITIVES

- Avoids first-pass metabolism
- Drug absorption is fast
- Rapid onset of action

NEGATIVES

- Generally considered unsuitable for prolonged administration
- Unpalatable & bitter drugs
- Irritation of oral mucosa
- Large quantities cannot be given
- Few drugs are absorbed
- Advantages lost if swallowed
- Dry mouth
- Few licensed products
Rectal

POSITIVES

• May circumvent first-pass elimination
• Effective absorption most meds used at end of life

NEGATIVES

• Uncomfortable (requires repeated movement)
• Ongoing invasion of privacy
• Low dose versatility – usually one drug, one dose
• Time to onset of effect
• Limited options
Successful use of pregabalin by the rectal route to treat chronic neuropathic pain in a patient with complete intestinal failure.

Doddrell et al. BMJ Case Rep 2015 pii: bcr2015211511

• 70-year-old patient with chronic neuropathic pain and complete intestinal failure
• Unclear if capsule was used, or novel formulation
• Patient’s pain scores improved after titration
Transdermal Opioids

**POSITIVES**

- Circumvents first-pass elimination
- Ease of use
- Extended duration of action
- Good patient compliance
- Painless administration

**NEGATIVES**

- Local irritation
- Use in patients with stable pain
- Temp affects absorption
- Patch may not adhere well
- Application may be difficult
**Intranasal**

**POSITIVES**
- Circumvents first-pass elimination
- Ease of use
- Rapid drug absorption and quick onset of action
- Painless administration

**NEGATIVES**
- Local irritation
- Small volume (0.2mL each nostril)
- May swallow dose – loss of effect
- Drug suitability
- Lack of evidence
Intranasal Ketamine and Its Potential Role in Cancer-Related Pain

- There are no data on intranasal ketamine for cancer-related pain!
- Intranasal ketamine may be an option for patients unable to tolerate oral administration
Not suitable for long-term management of cancer pain
Systematic review of the role of alternative application routes for opioid treatment for moderate to severe cancer pain: An EPCRC opioid guidelines project


• Good evidence that subcutaneous administration of morphine or other opioids is an effective alternative for cancer patients if oral treatment is not possible
Systematic review of the role of alternative application routes for opioid treatment for moderate to severe cancer pain: An EPCRC opioid guidelines project


- Intravenous, rectal or transdermal therapy will offer a good alternative to the subcutaneous route
- No significant differences in efficacy or adverse effects between the alternative application routes
Subcutaneous Administration of Drugs in Palliative Care: Results of a Systematic Observational Study

Bartz et al. J Pain Symptom Manage. 2014; 48(4) 540–547

- 120 patients, 3957 applications
- Subcutaneous administration of medication is a very flexible, broadly feasible, rather safe, and nonburdensome method of drug administration
- Needs appropriate nursing care, and requires standardised policies and procedures.
Continuous Subcutaneous Infusions

- Embraced by palliative care services in the UK
- Rectal administration is not always practical, or acceptable
- Intramuscular administration will be painful, especially if the patient is cachectic
- Intravenous injections or infusions
  - risk of infection
  - CSCIs are less invasive, yet as effective
- Repeated intermittent SC bolus injections through indwelling subcutaneous cannula possible
  - use of a CSCI is more practical
Continuous Subcutaneous Infusions

- The Smiths Medical (formerly Graseby) devices have been the mainstay of palliative care provision across the UK for 30 years.
Syringe Driver in Terminal Care

- The syringe driver is a valuable alternative to the less pleasant methods of drug administration
- The syringe driver is a major advance in the terminal care of patients
Continuous Subcutaneous Infusions

• Used in palliative care through serendipity
• Martin Wright’s GP & neighbour was Dr Patrick Russell
• During usual friendly discussion, idea of CSCI in palliative care was born
• Russell described 1st CSCI in the hospice context in 1979
• A CSCI remains popular to this day
Popularity of MS26 undoubtedly due to several factors:
- small size and weight (190 mm x 53 mm x 30 mm; 300g)
- increased mobility and independence for patient
- relatively simple to use (after training)

Manufactured in UK by Pye Dynamics (originally armaments); later Graseby (depth charges)
Continuous Subcutaneous Infusions

- 2003 – Medical Devices Agency
- These devices do not include many of the safety features which would be expected of current infusion technology
Continuous Subcutaneous Infusions

- MS drivers did not comply with IEC 60601-2-24
- Applied to the basic safety and essential performance of infusion pumps and controllers
What did IEC 60601-2-24 stipulate?

• Allows the user to set up an infusion over 24 hours quickly and reliably
• Delivery rate is calculated by the device
• Safety alarms:
  – power interruption
  – a blocked line
  – a displaced syringe
  – tampering with the infusion
  – end of infusion
## Continuous Subcutaneous Infusions

<table>
<thead>
<tr>
<th>Device</th>
<th>Graseby MS26/MS16A</th>
<th>CME T34</th>
</tr>
</thead>
<tbody>
<tr>
<td>List Price (ex VAT)</td>
<td>£850</td>
<td>£995</td>
</tr>
<tr>
<td>Meets IEC 60601-2-24</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>UK Launch</td>
<td>1976</td>
<td>2006</td>
</tr>
<tr>
<td>Size (H x W x D)</td>
<td>166 x 53 x 23</td>
<td>169 x 53 x 23</td>
</tr>
<tr>
<td>Weight with battery (g)</td>
<td>183</td>
<td>260</td>
</tr>
<tr>
<td>Lock box weight (g)</td>
<td>183</td>
<td>188</td>
</tr>
<tr>
<td>Battery</td>
<td>1x 9V Alkaline</td>
<td>1x 9V Alkaline</td>
</tr>
<tr>
<td>Battery life (days)</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Overall usability for palliative care applications</td>
<td>⭐⭐⭐⭐⭐</td>
<td>⭐⭐⭐⭐⭐</td>
</tr>
</tbody>
</table>
Continuous Subcutaneous Infusions

- 2002 – Amended Medical Devices Legislation
- New regulatory system for medical devices
- Current standards retained for 5 years to cover existing products (i.e. MS drivers)
- October 2007 – Smiths Medical voluntarily withdrew the devices from the Australian market
- At this time in the UK, ad hoc adoption causing problems across interfaces
Continuous Subcutaneous Infusions

- NPSA recommended syringe pumps with:
  - rate settings in millilitres (mL) per hour
  - mechanisms to stop infusion if the syringe is not properly and securely fitted
  - alarms that activate if the syringe is removed before the infusion is stopped
  - lock-box covers and/or lock out controlled by password
  - provision of internal log memory to record all pump events
Continuous Subcutaneous Infusions

- For IMMEDIATE ACTION by all organisations in the NHS and independent sector who use ambulatory syringe drivers
- Introduction of syringe drivers with additional safety features by Dec 2015
- This was EIGHT years after Australia & NZ acted
Medical Device Alert

MDA/2018/010    Issued: 28 March 2018 at 15:00

All T34 ambulatory syringe pumps – risk of unintended pump shutdown and delay to treatment

Summary

Manufactured by Caesarea Medical Electronics (CME) Ltd – a variation in battery size can cause problems with connections in the battery housing.
Thousands of elderly patients may have died prematurely because of cheap, faulty syringe pumps in a scandal described as “one of the biggest cover-ups” in NHS history.
Graseby MS 16A & MS 26 syringe drivers were loaded with capsules and programmed to release drugs into a patient’s bloodstream over an extended period so doctors and nurses did not have to inject manually.
The whistleblower, a senior Department of Health official, said: “Anyone who has lost their granny over the last 30 years when opiates were administered by this commonly used syringe driver will be asking themselves, ‘Is that what killed Granny?’”
Continuous Subcutaneous Infusions

- Bishop James Jones chaired the Gosport independent panel:

  “I understand the concerns about syringe drivers highlighted by The Sunday Times”
  “The panel was required to analyse historical documents relating to the early deaths from 1989 to 2000. None featured faulty syringe drivers.”
Continuous Subcutaneous Infusions

- Scaremongering needs addressing
- Questions do need answering
  - why did it take up to 8 years?
  - what was the scale of the problem?
  - who is the whistleblower and what facts/figures are being used?
• In 2007, the NPSA issued Patient Safety Alert 20

“Full technical information about stability in solution and compatibility information for commonly used mixtures in should be readily available”
Continuous Subcutaneous Infusions

- In 2008, MHRA issued a consultation document (MLX 356)
- The Commission on Human Medicine (CHM) advised the MHRA:

  “...research should be commissioned to develop authoritative national advice on mixing of medicines to encompass compatibility and stability data”
ChemdEL

Chemical compatibility of drugs administered by continuous subcutaneous infusion for end of life care
• **Incompatibility** - a theoretically reversible physicochemical change that may result in precipitation or insolubility, which may not always be visible
  – e.g. midazolam and dexamethasone

• **Instability** - irreversible chemical degradation of the active compound, resulting in loss of potency
  – e.g. glycopyrronium and dexamethasone
Influence of pH on midazolam (A) and the more soluble open-ring benzophenone (B)
Drug Compatibility

<table>
<thead>
<tr>
<th>Salt Ion Suffix</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>-ium –ate (organic anion)</td>
<td>Dexamethasone sodium phosphate</td>
</tr>
<tr>
<td>-ium (base anion)</td>
<td>Diclofenac sodium, phenobarbital sodium</td>
</tr>
<tr>
<td>-ate &amp; -ide (acid cations)</td>
<td>Cyclizine lactate, fentanyl citrate, morphine sulphate, octreotide acetate, alfentanil hydrochloride, hyoscine hydrobromide, levomepromazine hydrochloride, metoclopramide hydrochloride, oxycodone hydrochloride</td>
</tr>
<tr>
<td>-ate –ide &lt;br&gt; -ide &lt;br&gt; -ium –ate &lt;br&gt; -ium ide</td>
<td>denote quaternary ammonium cations &lt;br&gt; Hyoscine butylbromide &lt;br&gt; Glycopyrronium bromide</td>
</tr>
</tbody>
</table>
Drug Compatibility

- How many drug combinations are possible?
- 5 opioids (at least)
- 15 supportive drugs (at least)
- Typically 2 or 3 drugs plus opioid
Drug Compatibility

\[ C(n, k) = C_n^k = \binom{n}{k} = \frac{n!}{k!(n-k)!}. \]
Identification of drug combinations administered by continuous subcutaneous infusion that require analysis for compatibility and stability

Dickman et al. BMC Palliative Care (2017) 16:22

- National survey identified 40 commonly used combinations from \( \approx \) 2000 entries
- Delphi study identified 5 combinations
- Formed the basis of the analytical study
Analysis of the chemical compatibility and stability of drug combinations used in continuous subcutaneous infusions

Dickman et al. *Manuscript submitted*

- A total of 30 discrete combinations were analysed
  - 20 at max/min
  - 9 min
  - 1 max
Analysis of the chemical compatibility and stability of drug combinations used in continuous subcutaneous infusions

Dickman et al. *Manuscript submitted*

- All 30 combinations were shown to be physically and chemically compatible and stable over an infusion period of 24 hours under normal fluorescent light at ambient room temperature.
**ChemdEL Results**

**Morphine**
- Cyclizine
- Haloperidol
- Hyoscine butylbromide
- Metoclopramide (max only)
- Dexamethasone & Ranitidine
- Glycopyrronium Bromide & Midazolam
- Haloperidol & Hyoscine butylbromide
- Haloperidol & Midazolam (min only)
- Hyoscine butylbromide & Midazolam
- Levomepromazine & Midazolam (min only)
- Metoclopramide & Midazolam (min only)

**Oxycodone**
- Glycopyrronium bromide & Midazolam
- Haloperidol & Hyoscine butylbromide
- Haloperidol & Midazolam (min only)
- Hyoscine butylbromide & Midazolam
- Hyoscine butylbromide & Octreotide
- Ketamine & Levomepromazine
- Levomepromazine & Midazolam (min only)
- Metoclopramide & Midazolam(min only)
ChemdEL Results

Alfentanil

- Cyclizine
- Haloperidol
- Metoclopramide
- Midazolam
- Hyoscine butylbromide & Levomepromazine
- Hyoscine butylbromide & Octreotide
- Levomepromazine & Midazolam (min only)
- Metoclopramide & Midazolam
- Hyoscine butylbromide, Levomepromazine & Midazolam

Diamorphine

- Haloperidol & Midazolam (min only)
- Levomepromazine & Midazolam (min only)
Equianalgesia
Equianalgesic dose:

“... that dose at which two opioids (at steady state) provide approximately the same pain relief.”
Equianalgesia

- Morphine has poor and variable oral absorption
- Complicates conversion values
- No equianalgesic table can fully address all clinical factors that influence opioid pharmacology
- Most of the tables are derived from single-dose studies, expert opinion and studies in non-cancer patients
- Designing a study to adequately address all variables that influence equianalgesia would be extremely difficult if not impossible
Equianalgesia

- Alfentanil:Diamorphine SC
- Expert opinion derived 1:10\(^{(1)}\)
- Based on 4 patients
- Adopted as canon

- Recent retrospective review suggests equianalgesic ratio is closer to 1:6\(^{(2)}\)
- Based on 35 patients

Equianalgesia

• Bidirectional ratios safer?

• Alfentanil ⇄ Diamorphine SC
  – 1:6

• Diamorphine ⇄ Alfentanil
  – 10:1
• Morphine: Oxycodone
• Is oxycodone more potent than morphine?

• No – it isn’t. Approaching 1:1 \(^{(1)}\)
• Difference in oral conversion rate due to poor bioavailability of morphine
• Napp maintain 2:1 (25% vs 50%)

• BNF, PCF5 suggest 1.5:1

1. Dr K Smith. Director of Clinical Pharmacology Napp Personal communication. 2018
Equianalgesia

- Does cause confusion
- Several services produced 2 equianalgesic tables
  - specialist
  - generalist
- Equianalgesic ratio is simply a starting point
- Consider other factors before arriving at dose
  - co-morbidity
  - concurrent medication
Tonight
Britain on Painkillers: The Silent Epidemic
Series 20 - Episode 28 - Are we hooked on opioids?
Millions in Britain are taking powerful prescription painkillers that many experts argue are ineffective in reducing chronic pain.
Equianalgesia

- Ensure advice given about doses >120mg PO morphine/24hrs