The Use of Transdermal Opioids in Palliative Care

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• Introduction — Dr Graham Whyte
• Literature Review — Dr Paula Powell
• Guidelines and Standards - Dr Clare Littlewood
• Discussion
Introduction

- New long term audit
- No previous guidelines
- Anecdotal stories of incorrect usage/adverse effects
- Uncertainty for generalists
- Link with Chapter 19: ‘Guidelines for the use of Transdermal Fentanyl in the Dying Patients’ amalgamated at later date
Transdermal Opioids

Literature Review
Morphine is Gold Standard Opioid for Cancer Pain

Transdermal Opioids – How Do we view them?

- Niche market? - good in renal failure
- Stable pain?
- Oral route not possible?
- Other opioid toxicity?
- Compliance issues?
- Patient preference?
Transdermal Opioids

- Are they safe and efficacious?
- For whom and how should they be prescribed?
- How should conversions to and from other opioids be managed?
- What knowledge do generalists have of Transdermals?
Prescribing Data and Guidelines

- Palliative Care Formulary 3rd Edition (PCF3) - Twycross R, Wilcock A, Editors
Buprenorphine

• Love it or hate it?
Buprenorphine - Pharmacology

- Partial μ- opioid receptor agonist.
- K and δ opioid receptor antagonist.
- Physiological effects similar to morphine.
- Metabolised via the liver and inactive metabolites are excreted via faeces.

Side Effects - Common >10%

- Dizziness
- Drowsiness
- Headache
- Nausea and vomiting
- Local irritation
Side Effects - Uncommon <10%

- Anxiety
- Insomnia
- Asthenia
- Hypotension
- Fainting
- Oedema
- Anorexia
Buprenorphine

- Caution is suggested in patients with severe hepatic dysfunction but not mild-moderate.
- CYP3A4 inhibitors may increase levels.
- Safe in renal failure- not removed by haemodialysis.
- Slows intestinal transit- constipation less than with morphine.

Buprenorphine

- Indications: moderate to severe cancer pain not responding to non-opioid analgesics. Intolerance to other opioids
- Contra-indications: TD route should not be used for acute (transient, intermittent or short term pain) or for rapid dose titration for severe uncontrolled pain.

**Buprenorphine**

- **Butrans®** = 7 day patch 5mcg, 10mcg, 20mcg/hr
- **Transtec** = 96 hour patch 35mcg, 52.5mcg, 70mcg/hr.
- Absorption increased by heat.
- Buprenorphine equianalgesia with PO morphine varies in literature from 75:1 to 115:1
## Morphine Equivalents

<table>
<thead>
<tr>
<th>Transtec</th>
<th>TTD oral morphine</th>
<th>Butrans®</th>
</tr>
</thead>
<tbody>
<tr>
<td>- - - -</td>
<td>10-20mg</td>
<td>5mcg</td>
</tr>
<tr>
<td>- - - -</td>
<td>40-60mg</td>
<td>20mcg</td>
</tr>
<tr>
<td>35mcg</td>
<td>60-100mg</td>
<td>- - - -</td>
</tr>
<tr>
<td>70mcg</td>
<td>120-200mg</td>
<td>- - - -</td>
</tr>
<tr>
<td>140mcg</td>
<td>240-380mg</td>
<td>- - - -</td>
</tr>
</tbody>
</table>

Merseyside and Cheshire Palliative Care Network audit Group 
Standards and Guidelines 4th Ed. 2010 
PCF3 recommends 100:1 conversion
Commencing Patches - Weekly or 96 Hourly

- Systemic analgesic concentrations reached within 12-24 hours.
- Levels continue to rise for 32-54 hours.
- Steady state may not be reached for 9 days for higher doses.
- If satisfactory analgesia not achieved after 72 hours then next patch strength should be used.
Buprenorphine - Breakthrough

- Morphine and other μ- opioid receptor agonists are acceptable for breakthrough. Without loss of analgesia.
- Antagonism does not occur at normal clinical doses.
Breakthrough Analgesia

- $1/6^{th}$ equivalent TDD oral morphine as NR formulation or other opioid in appropriate dose.
- Sublingual buprenorphine starting dose $= 200 \text{mcg} = 15 \text{mg}$ morphine. Longer acting than morphine.
- Repeat 6-8 hourly.
Buprenorphine-Respiratory Depression

- Rare in recommended doses.
- Ceiling effect for respiratory depression.
- Naloxone is required in higher doses (up to 50%) to reverse effects because of strong receptor affinity.
- Bolus Naloxone may not reverse respiratory depression. (Level 3).

Daha A. Palliative Medicine 2006; 20:s3-s8
Is Buprenorphine Safe and Efficacious for Patients with Cancer Pain?

- Review of evidence - Transdermal buprenorphine has superior safety in respect to respiratory depression, immunological and renal effects over other step III opioids. (level 2+)
- RCT buprenorphine/placebo patches 289 patients. Poulain et al. (level 2+)

Is Buprenorphine Efficacious?

- Multicentre, open label, uncontrolled, prospective, observational study. 1223 patients recruited non cancer and cancer pain. Dose range 35-70mcg. 1st line step III opioid. Significant increase in number reporting good or very good pain relief from baseline.

- 44% drop out. (level 2+)

Muriel C et al Clinical therapeutics 2005;27(4) 451-462
Fentanyl

- μ-opioid receptor agonist.
- Lipophylic
- Metabolised in the liver to norFentanyl-safe in renal failure.
- Caution with CYP3A4 inhibitors/inducers.
- Action supraspinally- minimal distribution in vascular system (unlike morphine).
Fentanyl – Side Effects

- Sedation
- Nausea and vomiting
- Constipation
- Delirium
- Dry Mouth
- Neurotoxic effects e.g. Myoclonus, hallucinations.
- Respiratory depression
Transdermal Fentanyl

- Indications- moderate - severe chronic pain including cancer and AIDS related pain.
- Severe chronic pain (BNF).
- Contraindications- nil absolute but should not be used for acute (transient, intermittent or short term pain).

British National Formulary March 2010
Fentanyl in Palliative Care

- Strong opioid, WHO analgesic ladder step III.
- Use when step II fails.
- Stable severe pain, swallowing difficulties, intractable nausea or vomiting.
- Renal failure eGFR < 30.

SIGN Guidelines 106 - Control of Pain in Adults with Cancer
Transdermal Fentanyl

- Available as reservoir and matrix patches 12, 25, 50, 75, 100 micrograms/hr
- Reservoir- generic products, Tilofyl. Release controlled by rate limiting membrane.
- Matrix- Durogesic®, DTrans and Matrifen®. Drug held in an adhesive matrix.
- Patches are bio-equivalent.
- Absorption can be increased by heat.
- Good practice to prescribe by brand.
# Fentanyl Pharmacokinetics

<table>
<thead>
<tr>
<th>Onset of action</th>
<th>3-23h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak plasma concentration</td>
<td>24-72 hours</td>
</tr>
<tr>
<td>Plasma half life</td>
<td>13-22h</td>
</tr>
<tr>
<td>Duration of action</td>
<td>72 hours (48 in some)</td>
</tr>
</tbody>
</table>

- **Onset of action**: Time required for the drug to exert its primary effect.
- **Time to peak plasma concentration**: Time taken for the maximum concentration of the drug to reach the bloodstream.
- **Plasma half life**: Time it takes for the drug concentration to reduce by half in the bloodstream.
- **Duration of action**: How long the drug remains effective after administration.
## Equianalgesia with Morphine

<table>
<thead>
<tr>
<th>TDD oral morphine</th>
<th>Transdermal Fentanyl 72 hourly</th>
</tr>
</thead>
<tbody>
<tr>
<td>30mg</td>
<td>12mcg</td>
</tr>
<tr>
<td>60mg</td>
<td>25mcg</td>
</tr>
<tr>
<td>120mg</td>
<td>50mcg</td>
</tr>
<tr>
<td>180mg</td>
<td>75mcg</td>
</tr>
<tr>
<td>240mg</td>
<td>100mcg</td>
</tr>
<tr>
<td>720mg</td>
<td>300mcg</td>
</tr>
</tbody>
</table>

Merseyside and Cheshire Palliative Care Network Group Equianalgesic Table
Breakthrough Analgesia

- Prescribe 1/6\(^{th}\) of the equivalent oral TDD morphine or other opioid.
- Immediate release formulations of Fentanyl e.g. Abstral\(^{®}\) must be titrated.
Is Transdermal Fentanyl Safe and Efficacious?

- Systematic review of literature 1966-2007. 3 RCTs comparing TD Fentanyl with oral morphine.
- No difference in overall adverse effect profile, or efficacy.
- Reduction in constipation.
- Patient preference in favour of Fentanyl. (level 1+)

Fentanyl Comparison with Morphine

- Randomised, open, crossover study with morphine.
- Equally efficacious
- Fentanyl caused significantly less constipation and daytime drowsiness. (level 2+)

Fentanyl – Morphine-Methadone

- 3 year RCT 108 patients with advanced cancer. Randomised to receive Fentanyl, morphine or methadone when weak opioids had failed.
- No difference in pain intensity, QOL, use of additional analgesia, Fentanyl most expensive.

Transdermal Fentanyl - Concerns

- Informed prescribing is essential.
- 3 case reports of inappropriate prescribing of Transdermal Fentanyl by clinicians.
- 84 year woman commenced on 50mcg patch from paracetamol/codeine. (level 3)

Transdermal Fentanyl - Concerns

- Research showing that Transdermal Fentanyl is safe has usually been conducted by pain specialists.
- Education is critical to ensure that Transdermal Fentanyl is prescribed appropriately and safely.
- All doctors should only use drugs with which they are familiar.
National Safety Alerts- FDA 2005

- Series of significant adverse events (toxic SE and deaths) in USA relating to Transdermal Fentanyl.
Conclusions of Investigation into Deaths

- Lack of appreciation that Fentanyl is a strong opioid.
- Inappropriate use for acute pain.
- Lack of patient awareness of safe use, avoid heat sources, signs of overdose.
- Lack of awareness of potential drug interactions.
FDA Update 2007

- Transdermal Fentanyl should not be initiated in opioid naive patients.
- Patients should have received strong opioids to the equivalent of 60mg TDD oral morphine for > 1 week.
- Must not be initiated for titration.
UK Alerts

- Medicines and Healthcare products Regulatory Agency MHRA- Fentanyl Patches September 2008
Factors Identified

- Dosing errors by healthcare professionals, patients or care givers.
- Accidental exposure.
- Exposure to heat resulting in increased absorption.
- Inappropriate prescribing in opioid-naive patients.
Generalists Knowledge

- Survey questionnaire to GPs, hospital consultants and oncologists. Assessed knowledge of the use of Transdermal Fentanyl in clinical practice.
- Overall knowledge and confidence in using Transdermal Fentanyl was poor.

Summary

- Transdermal opioids are a useful addition to the armamentarium of analgesics.
- They are effective in controlling moderate to severe pain.
- They are acceptable to patients and in controlled studies had no more side effects than other opioids.
Summary

- There is evidence from prescribing surveillance that incorrect use of Fentanyl can cause harm to patients.
- There is some evidence from case reports that inappropriate prescribing can cause harm to patients.
- There is some evidence that generalists have poor knowledge of the prescribing of Fentanyl
General Principles

- All patients prescribed Transdermal opioids should have a pain assessment in accordance with accepted principles of pain management(1)
- Patients should be given information regarding their strong opioid and the known side effects(2,14,15)
- It is good practice to brand when prescribing Transdermal opioids eg Butrans®, Durogesic-D® trans(19)
• Reservoir patches should not be cut due to rapid release of opioid. Matrix patches can be cut although not recommended by manufacturers (5)
• Patients may experience opioid withdrawal symptoms (gastric flu) when changed from another opioid to Transdermal (3,4)
Guidelines

- Transdermal opioids are contra-indicated in patients with acute pain and in those who need rapid dose titration for severe uncontrolled pain (1,8) [Level 3]
- Patients not previously receiving opioids should start on lowest buprenorphine patch or patients with unrelieved pain despite maximum step 2 analgesic should start on 25 or 35mcg/hr. For Fentanyl patients on maximum step 2 opioids should start on 12mcg/h (5) [Level 3]
Systemic analgesic concentrations are generally reached within 12 hrs; so when converting from 4hrly PO morphine give 4hrly doses of morphine for first 12 hrs after applying patch. 12hr mr morphine apply patch and final dose at same time. 24hr mr apply 12 hrs after final dose CSCI continue syringe driver for 12 hrs after applying patch(5) [Level 3]

Appropriate breakthrough medication dose should be decided using equi-analgesic tables. Steady state concentrations not reached until 36-48hrs after first application so patient should use liberal p.r.n doses during first 24 hrs See table1(1,5) [Level 3]
<table>
<thead>
<tr>
<th>PO morphine 4 hrly</th>
<th>Bu trans weekly</th>
<th>Transtec 96 hrly</th>
<th>Fentanyl 72 hrly</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5 mg</td>
<td>5-10mcg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5-10 mg</td>
<td>20mcg</td>
<td>-</td>
<td>12mcg</td>
</tr>
<tr>
<td>10-15mg</td>
<td>-</td>
<td>35 mcg</td>
<td>25mcg</td>
</tr>
<tr>
<td>15-25mg</td>
<td>-</td>
<td>52.5mcg</td>
<td>50mcg</td>
</tr>
<tr>
<td>20-30mg</td>
<td>-</td>
<td>70mcg</td>
<td>75mcg</td>
</tr>
<tr>
<td>40mg</td>
<td>-</td>
<td>140 mcg</td>
<td>100mcg</td>
</tr>
</tbody>
</table>
• For patients taking morphine that is not dose equivalent it is appropriate to opt for patch that is slightly more or less depending on whether patient is pain free or still in pain(5) [Level 4]
• When switching opioids due to toxicity consider dose reduction of 25-50%(9,10,11) [Level 3]
• After 72 hrs if patient needs 2 or more doses analgesic/ day next strength patch should be used(5)[ Level4)

• Up to 25% patients using Fentanyl may need patch change every 48 hrs(12)( Level 4)

• In dying patients Transdermal patch should remain in place and appropriate as required doses of immediate release opioid prescribed(6)[Level 4] Please see guidelines for use of drugs in last hours of life for further information
Transdermal opioids are less constipating than morphine; halve the dose of laxative when starting and titrate according to need (5).

Transdermal opioids cause less nausea and vomiting than morphine but if necessary, prescribe haloperidol 1.5mg stat and on for one week then p.r.n [Level 4]
• In febrile patients the rate of absorption of Transdermal opioids increases and can cause toxicity. Absorption may be also enhanced by external heat sources. Patients should be warned about this. They may shower but should not soak in hot bath (5)[Level4]
Questions

- What do we mean by toxicity?
- How should we manage toxicity due to use of a Transdermal patch? Reduce by 25% 50%? Remove patch? Rotate opioid?
- Which opioid should we recommend for breakthrough? Pain.
Questions

- What is the role of Butrans® in cancer pain?
- What information should be given to patients about Transdermal opioids.
Standards

• All patients prescribed Transdermal opioid should have reason documented in notes(13) [Grade D]

• Transdermal opioids should not be used for acute pain and those who need rapid dose titration(1,8) [Grade C]
• Conversion from oral opioids should be used with reference to equi-analgesic tables (1,5)
[ Grade D]

• All patients with Transdermal opioids should have appropriate breakthrough analgesia prescribed (1,5) [ Grade D]
References


2. SIGN Guideline no 106: Control of pain in adults with cancer.


8. Quigley C. Opioid switching to improve pain relief and drug tolerability. The Cochrane database of systematic reviews 2004(3) Art no:CD004847.DOI:10.102/14651858CD 004847


References

14. USA Food and drug Agency: Safety warning on Fentanyl skin patches 2007