How should conversion from oral morphine to fentanyl patches be carried out?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals
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Background

Fentanyl patches are an effective alternative to oral morphine and a common question is how to change a patient from oral morphine to a fentanyl patch (1). Fentanyl patches are indicated in patients with stable pain who have difficulty swallowing, unacceptable side effects with oral morphine or other opiates e.g. oxycodone, hydromorphone; renal failure, persistent nausea and vomiting, gastrointestinal obstruction or poor compliance with oral medication (2,3). Each new patch is applied for 72 hours and provides continuous delivery of fentanyl (2). Fentanyl patches are not suitable for acute pain or for patients who have rapidly changing analgesic requirements because the long time to steady state prevents rapid titration of the dose (4).

The National Patient Safety Agency issued a rapid response report in July 2008 aimed at reducing dosing errors with opioid medicines (5). This highlights dose conversion as one of the areas where prescribing errors can occur (5). It states: “where a change in formulation or medicine is required, practitioners inexperienced in the use of opioids should use references for dose conversion to aid calculation of a safe dose”(5).

Answer

Advice on equivalent potencies of oral morphine and transdermal fentanyl

Manufacturers list a wide range of oral morphine doses corresponding to each fentanyl patch strength, with a resultant wide range in conversion ratios of oral morphine to transdermal fentanyl (approximately 75:1 to 223:1) (2,6,7,8,9,10,11,12). Studies confirm the wide range in conversion ratios and note that ratios that are conservative in one direction may be excessive in the reverse (2,13). Direct conversion from oral morphine to transdermal fentanyl with a ratio of oral morphine to transdermal fentanyl of 100:1 was examined in 98 patients with cancer pain (14). Regression analysis at the end of the study revealed a mean oral morphine to transdermal fentanyl ratio of 70:1 (14). However, the authors concluded that a calculation table for the conversion of oral morphine to transdermal fentanyl with a ratio of 100:1 is safe and effective (14). Although this is lower than the true ratio determined in the study, it implies a sufficient margin for safety and may avoid overdoses caused by inter-individual differences in response to different opioids (14). A conversion ratio of 100:1 is also endorsed by the Palliative Care Formulary (PCF), a resource about the use of medicines in palliative care and the British National Formulary (BNF) (3,4). However, manufacturers guidance and some local guidelines advocate a range of conversion ratios to avoid overdosing patients (6,7,8,9,10,11,12,15). NICE advise to use caution when calculating opioid equivalence for transdermal patches: A transdermal fentanyl 12 microgram patch equates to approximately 45 mg oral morphine daily(16).

Comparative doses of oral morphine to transdermal fentanyl are given in Table 1. The dose conversion used in this table of oral morphine: transdermal fentanyl demonstrates the ratio advocated in practice of 100:1 (recommended by the BNF and PCF). The Summary of Product Characteristics (SPC) for the specific fentanyl patch being used should also be consulted. The dose conversions advised vary between SPCs and may be up to 223:1. This is an approximate guide only as comprehensive data are lacking and there is inter-individual variation. Patients who are taking a daily dose of morphine that falls between fentanyl patch strengths will need to be changed to a patch which is either slightly less or slightly more potent than the morphine dose (3). This will be a clinical decision. In practice, many clinicians start at a lower dose and titrate with oral morphine (15). It is advisable to establish the exact analgesic requirement before initiating or changing the patch strength (15). If switching because of possible opioid-induced hyperalgesia, reduce the calculated equivalence by 25-50% (3).

From the NHS Evidence website www.evidence.nhs.uk
Patients will require frequent reassessment of efficacy and adverse effects and dose titration after patch initiation or dose change as well as a short acting opioid for breakthrough pain (2). Steady state concentrations of fentanyl are reported as being achieved after approximately 36 to 72 hours (3,17). The patient should use breakthrough analgesia as needed for the first 3 days particularly the first 24 hours (3). Appropriate doses of morphine are given in Table 1.

If the patient requires two or more rescue doses of morphine per day after 48 hours, the strength of the next patch to be applied (after 72 hours) should be increased by the equivalent patch strength (usually 12-25 micrograms/hour) (3,15). Dose adjustment is not recommended more frequently than every 72 hours and dose titration should be limited to increments of 12 or 25 micrograms/hour as appropriate (3,13).

Table 1: Conversion doses from oral morphine to transdermal fentanyl based on the dose ratios 100:1 (adapted from the PCF and the BNF) (3,4)

Note: this table should be used in conjunction with Summary of Product Characteristics for the fentanyl patch being used

<table>
<thead>
<tr>
<th>Oral 24-hour morphine (milligrams/day)</th>
<th>Transdermal fentanyl (micrograms/hour)</th>
<th>milligrams/24hours advised in PCF a</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>12</td>
<td>0.3</td>
</tr>
<tr>
<td>60</td>
<td>25</td>
<td>0.6</td>
</tr>
<tr>
<td>120</td>
<td>50</td>
<td>1.2</td>
</tr>
<tr>
<td>180</td>
<td>75</td>
<td>1.8</td>
</tr>
<tr>
<td>240</td>
<td>100</td>
<td>2.4</td>
</tr>
</tbody>
</table>

a. using traditional 1/6 of total daily dose as when required dose

More than one fentanyl patch may be used for dose adjustments and for doses greater than 100 micrograms/hour (4,11). However, they should be applied at the same time to avoid confusion (4).

When should the regular oral morphine be stopped following the initiation of fentanyl patches?

Effective systemic analgesic concentrations of fentanyl are usually reached less than 12 hours after applying the patch (3). When converting oral morphine to transdermal fentanyl:

- if taking 4 hourly oral morphine, continue giving regular doses for 12 hours after applying the fentanyl patch
- if taking 12 hourly modified release morphine, give the last dose and apply the first fentanyl patch at the same time
- if taking 24 hourly modified release morphine, apply the first fentanyl patch 12 hours after the final modified release dose (2,3).
Are there any other factors to consider when switching from oral morphine to fentanyl patches?

- Fentanyl is less constipating than morphine (3,14). Therefore, when patients are converted from morphine to fentanyl, the dose of laxative(s) may need to be reduced and subsequently adjusted according to need (3,15).
- Patients may suffer from withdrawal symptoms (e.g. restlessness, diarrhoea, colic, nausea, sweating) despite satisfactory pain relief (3,11). These symptoms can be treated with rescue doses of morphine until they resolve after a few days (3).
- Since peak fentanyl levels occur after 12 to 24 hours of treatment, monitoring of the patient for adverse events, which may include hypoventilation is recommended for at least 48 hours after initiation of transdermal fentanyl or up-titration of the dose (11).
- Healthcare professionals should ensure patients and caregivers are aware of signs and symptoms of fentanyl overdose i.e. trouble breathing or shallow breathing; tiredness; extreme sleepiness or sedation; inability to think, walk or talk normally; and feeling faint, dizzy or confused. Patients and caregivers should be advised to seek medical attention immediately if overdose is suspected (18). Fentanyl toxicity may be more subtle than morphine toxicity due to a lack of hallucinations, myoclonus etc. and can present as vagueness, drowsiness or not feeling well (17).
- When a fentanyl patch is removed a subcutaneous depot remains (2). Serum concentrations fall gradually, decreasing by 50% in 16 hours (range 13 to 22 hours) (2). Patients who experience serious adverse effects should have patches removed immediately and should be monitored for up to 24 hours after the patch is removed (18).
- Increased body temperature, exposure of patches to external heat sources, and concomitant use of CYP3A4 inhibitors may lead to potentially dangerous increases in serum fentanyl levels. Concomitant use of other CNS depressants might also potentiate fentanyl adverse effects (18).
- There are two different formulations of fentanyl patch i.e. reservoir and matrix which can be supplied against a direction for fentanyl patch. Where possible patients should be maintained on the same formulation (15).
- Abuse potential of reservoir patches should be a consideration in areas of high drug diversion (15).
- NICE Guidance states: "Consider initiating transdermal patches with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are stable, supported by specialist advice where needed" (16).

Summary

- Data from a small study has shown that conversion of oral morphine to transdermal fentanyl with a ratio of 100:1 is safe and effective. This ratio is also endorsed by the Palliative Care Formulary and the British National Formulary. This differs from ratios recommended in some UK Summary of Products Characteristics. The decision regarding which conversion ratio to use should be based on patient specific factors, the level of patient monitoring which can be offered and the clinical setting.
- Comparative doses of oral morphine and transdermal fentanyl are given in Table 1. This should be used in conjunction with the Summary of Product Characteristics for the fentanyl patch being used.
- Patients who are taking a daily dose of morphine that is not exactly equivalent to a particular fentanyl patch strength, will need to be changed to a patch which is either slightly less or slightly more potent than the morphine dose. This will be a clinical decision based on patient specific factors and patients should be monitored.
- Effective systemic analgesic concentrations of fentanyl are reached less than 12 hours after applying the patch. Guidance is given above regarding the discontinuation of the regular morphine dose.
Medicines Q&As

- Patients will require frequent reassessment of efficacy and adverse effects and dose titration after patch initiation or dose change as well as a short acting opioid for breakthrough pain.
- Steady state concentrations of fentanyl are reported as being achieved after approximately 36 to 72 hours. The patient should use breakthrough analgesia as required for the first 3 days particularly the first 24 hours.
- The dose of laxative(s) may need to be reduced and subsequently adjusted according to need as fentanyl is less constipating than morphine.

Limitations
Caution is needed when converting patients between oral morphine and transdermal fentanyl. The conversion ratios given are an approximate guide only because of:
- wide inter-individual variation in opioid pharmacokinetics (3)
- variables such as concurrent medication and nutritional status (3)
- interproduct variability and generic prescribing of fentanyl products
- a lack of comprehensive trial data

The data presented are derived from adults and may not be applicable to children. The information in this Q&A should be used in conjunction with the relevant Summary of Product Characteristics.

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References

From the NHS Evidence website www.evidence.nhs.uk


15. Specialist palliative care pharmacist, The Royal Marsden NHS Foundation Trust formally working at St Peters Hospice. Personal communication 19/3/2010 and 19/7/2012


Quality Assurance

Prepared by
Emma Templeman, South West Medicines Information & Training, Bristol

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Checked by
Julia Kuczynska, South West Medicines Information & Training, Bristol

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- Medline (exp fentanyl AND exp morphine AND exp administration, cutaneous)
- Specialist palliative care pharmacist, The Royal Marsden, London.

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