Rapid-onset opioids and the management of episodic pain

Paul Howard BMedSci, MRCP and Rachel Howard PhD, MRPharmS, DipClinPharm

This is the fourth in a series of articles that focus on what GPs should consider when monitoring and prescribing specialist-initiated palliative-care medicines. Here, the authors summarise the key issues around the use of rapid-onset opioids in palliative care.

KEY POINTS

- Rapid-onset opioids are used for episodic pain unresponsive to conventional approaches; they are initiated by specialists because:
  - dose titration differs from more familiar opioids
  - they should be considered alongside several other ‘specialist-only’ options (see Table 3)
- Rapid-onset fentanyl: 5 preparations are available (Abstral, Actiq, Effentora, Instanyl, PecFent); they are:
  - licensed for cancer-related breakthrough pain
  - suggested to give a moderately faster analgesic onset (this is open to question; see text)
  - not bioequivalent (patients should not be switched between preparations without retitration)
  - significantly more expensive; all are flat-priced across different dose sizes (eg, giving 2x100µg tablets per dose is twice as expensive as switching to 1x200µg-size tablet)
- Sublingual alfentanil spray has a shorter half-life and is thus sometimes used in place of fentanyl preparations where a shorter duration of action is desirable; however, it is unlicensed and has not been examined in any RCT; it is cheaper than fentanyl and more expensive than oral morphine
- Both fentanyl and alfentanil are more susceptible to drug interactions

This is the fourth in a series of articles that highlight some of the important issues for GPs to consider when their patients are started on specialist palliative-care medicines. These articles will help GPs to understand the purpose of some specialist palliative-care medicines and how to safely monitor and (if necessary) prescribe them.

Our recommendations are based on evidence from the literature wherever possible. Where there is insufficient information in the literature, our recommendations are based on the practice of one of the authors (PH).

Introduction

Rapid-onset opioids (ROOs) are claimed to act more quickly than conventional oral opioids such as oral morphine solution. They are thus a treatment option for transient increases in pain level (‘episodic pain’).

This article defines episodic pain, describes ROOs and their differences from oral morphine, presents an overview of episodic pain management and the place of ROOs within it, and concludes with important prescribing and monitoring considerations if ROOs are used.

What is episodic (‘breakthrough’) pain and why is it difficult to manage?

Episodic (‘breakthrough’) pain is a transient increase in pain level despite adequately controlled background (constant) pain.1-2 It:
- may follow a predictable trigger, eg, movement (incident pain) or dressing changes (procedural pain), or occur spontaneously
- is associated with poorer pain control and quality of life
- sometimes requires a different approach to the conventional management of continuous background pain.

Effective treatment of background pain remains important: around half of patients with episodic pain will achieve satisfactory pain control through use of conventional regular opioids and adjuvants.3 However, for others it can be difficult to give sufficient regular opioids to treat the episodic ‘peaks’ without causing drowsiness during the intervening ‘troughs’.

Additional analgesia, eg oral morphine, is sometimes given pre-emptively
or during pain episodes. However, for some patients the pain’s rate of onset and duration make oral morphine ineffective: it may act too slowly and/or for too long resulting in inadequate analgesia during the pain and/or drowsiness after the pain, respectively.

ROOs attempt to solve the first of these problems by acting more quickly.

What are rapid-onset opioids?
ROOs are opioids that are claimed to act more quickly than oral morphine (see Table 1). Current preparations contain either fentanyl or alfentanil in a spray, lozenge or rapidly dissolving tablet. Their high fat solubility allows direct absorption through the oral or nasal mucosa.

Five such fentanyl preparations are licensed for cancer-related episodic (‘breakthrough’) pain: a sublingual tablet (Abstral), a buccal tablet (Effentora), a lozenge (Actiq) and two nasal sprays (Instanyl, PecFent). They use a variety of approaches to optimise transmucosal absorption including pH adjustment (to minimise ionisation, thus maximising fat solubility) and pectin-based gel formation (to hold the drug for longer against the mucosa).

Alfentanil was used for the same indication prior to the advent of the above fentanyl products. It is given in a rapidly absorbed unlicensed sublingual spray (the only licensed preparation – Rapifen – is for intravenous use).

Although it probably acts no more quickly than licensed fentanyl alternatives, it may retain a place in pain management: its shorter duration of action might be better suited to patients with short-lived episodic pains, particularly if drowsiness arises from fentanyl’s longer half-life (see Table 1). However, it has never been examined for this indication in an RCT – use is almost entirely based on clinical experience.

How do ROOs differ from oral morphine?
ROOs differ in how they are dosed and used, their cost and propensity to interactions
ROOs have:
• a greater susceptibility to drug interactions (see Table 2)
• higher acquisition costs (prn fentanyl costs between £3.80 and £6 per dose; alfentanil’s price varies: it is available as a ‘special’ at a fixed price from a hospital manufacturing unit but is generally cheaper than prn fentanyl and more expensive than oral morphine)
• differing half-lives (morphine 1.5–4.5h, fentanyl 2.6–25h, alfentanil 1h – see Table 1).

ROOs are dosed differently. While oral morphine is conventionally given at a dose between a sixth and a tenth of the total daily morphine dose, ROOs require separate titration.

This reflects trial evidence that the effective ROO dose does not reflect the regular opioid dose. It may be because they are being used for different pains and highlights that the dose of oral morphine might also require individualisation rather than being rigidly based on a ratio with the regular dose. The latter practice arose from the tradition of titrating with four-hourly morphine liquid, with an extra (same) dose in between if required.

GPs will be familiar with using prn oral morphine requirements to guide the titration of regular sustained-release opioids to control background pain.

However, if the patient’s background pain is already well controlled by the regular opioid dose and additional opioid doses are for episodic pain, it is sometimes preferable not to ‘add in’ the extra dose to the regular opioid: the episodic and background pains are thus managed separately. This reduces the risk of unnecessary drowsiness or other toxicity in between episodes of pain.

Are ROOs really faster acting than oral morphine and other oral opioids?
Fentanyl Three RCTs attempted to compare the onset time of prn fentanyl with oral morphine or oxycodone. Although fentanyl appeared to bring relief moderately faster, the doses used may not be comparable.

The benefit was sustained throughout the total 60 minutes observation time suggesting that a relatively higher dose, rather than faster absorption, of fentanyl accounted for at least part of the difference.
Indeed, morphine’s time to maximum absorption is comparable to all except, perhaps, the intranasal preparations (see Table 1). Thus whether fentanyl-based ROOs are significantly faster acting than oral morphine remains in doubt.

*Alfentanil* Despite favourable reports of sublingual alfentanil use, it has not been examined for breakthrough pain in an RCT. Further, the available data describe intranasal rather than sublingual administration: intranasal alfentanil was as effective as iv alfentanil for post-operative pain in an RCT (*n*=40); in healthy volunteers, intranasal alfentanil is maximally absorbed within nine minutes; its half life was one hour.

**Duration of action compared to oral morphine**

The RCTs comparing fentanyl with oral morphine and oxycodone did not specifically examine the possibility that fentanyl’s longer half-life may be problematic.

Fentanyl’s pharmacokinetic properties raise the possibility of a much longer duration of action that might make it inferior to oral morphine for patients experiencing postdose drowsiness with oral morphine after pain subsides.

Although alfentanil’s shorter half-life might suggest a potential advantage in such circumstances, this possibility of reduced postdose drowsiness has not been confirmed in an RCT.

**What is the place of ROOs relative to other options?**

ROOs may be used where episodic pain is:

- opioid responsive and
- persists despite optimally managed background pain and
- a more rapid onset is needed than can be achieved with oral morphine and
- there are no alternative nonopioid or specialist options that are more appropriate, eg surgery or radiotherapy for the underlying causes, neuropathic pain treatments, nerve blocks.

They are thus not first-line options and are one part of a stepwise approach to the management of episodic pain, summarised in Table 3. ROOs can be unnecessary or ineffective if commenced without such a stepwise approach, eg ROOs, like other opioids, are unlikely to bring relief if neuropathic pain or skeletal spasm has not been identified and treated.

ROOs may also have a place for patients unable to swallow or absorb conventional oral opioids.

**Can GPs prescribe ROOs?**

Most of the steps described in Table 3 will be familiar to GPs. However, the titration of ROOs differs considerably from conventional opioids. Further, their use needs to be weighed against other potential ‘specialist’ alternatives and take account of background opioid doses.

Thus GPs without a special interest in pain management are advised to seek advice from a pain or palliation specialist before initiating a ROO.

However, GPs may be asked to take over the prescribing of a ROO once titrated to an effective dose in a specialist setting. If taking over prescribing is considered to be in the patient’s best interests, the same principles apply as described in previous articles. Therefore, GPs should:

- be confident that the recommended dose is safe; doses vary considerably between patients and between preparations; compare the patient’s dispensed medication with that described in the discharge letter and shared-care agreement
- know which preparation is being used: *do not switch between brands – they are not bioequivalent and serious or fatal toxicity can occur*.

- be confident that they will receive ongoing support from the specialist initiating the ROO
- determine whether the benefits to the patient outweigh the risks of taking over prescribing the ROO. For example, attending hospitals will be onerous for some patients, eg with movement-induced pain, and there are risks in prescribing unfamiliar medicines, particularly in the absence of good communication between the GP and specialist
- be familiar with which adverse effects and drug interactions to monitor for and how to manage them should they arise (see Table 2)

- be clear about their responsibility in the shared care of the patient; good communication can be supported with written shared-care agreements (examples for sublingual alfentanil are available from www.palliativedrugs.com)

- only take over prescribing if there is enough information to safely manage it; if a GP needs more information they should contact the referring specialist

GPs may also wish to seek advice from their pharmaceutical adviser about how their locality is approaching the relative cost impact on primary and secondary care, particularly with regard to fentanyl.

**Monitoring issues – interactions, switching preparations, adverse effects**

Whether or not they take over prescribing, GPs encountering patients receiving

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Time to maximum absorption (mins)</th>
<th>Bioavailability (%)</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>oral morphine solution</td>
<td>15–60</td>
<td>35</td>
<td>1.5–4.5</td>
</tr>
<tr>
<td>Abstral</td>
<td>40–120</td>
<td></td>
<td>5.4–6.3</td>
</tr>
<tr>
<td>Actiq</td>
<td>20–40</td>
<td>50</td>
<td>3.2–6</td>
</tr>
<tr>
<td>Effentora</td>
<td>35–96</td>
<td>65</td>
<td>2.6–20</td>
</tr>
<tr>
<td>Instanyl</td>
<td>13–24</td>
<td>89</td>
<td>3.2–4.3</td>
</tr>
<tr>
<td>PecFent intranasal alfentanil</td>
<td>15–20</td>
<td>-</td>
<td>15–25</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>65</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. Summary of pharmacokinetic properties most available data for alfentanil are based on intranasal administration in healthy volunteers, whereas sublingual administration is more commonly used in clinical practice.
<table>
<thead>
<tr>
<th>Problem</th>
<th>Explanation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Switching fentanyl preparations</strong></td>
<td>the 5 available fentanyl preparations are not bioequivalent; fatalities have occurred when switching between them(^\text{15})</td>
<td>a joint approach to medicines management across primary and secondary care can ensure consistency of preparation(s) and supporting pathways, eg shared-care agreements; prescribe using the brand name to avoid unintentional switching.</td>
</tr>
<tr>
<td><strong>Availability of alfentanil preparations</strong></td>
<td>sublingual alfentanil spray is an unlicensed ‘special’; community pharmacies may require additional information to source it</td>
<td>a joint approach to medicines management across primary and secondary care can ensure that shared-care agreements include information for community pharmacies on obtaining the most cost-effective supplies (prices vary widely) and emphasise to patients that they need to allow extra time when requesting repeat prescriptions</td>
</tr>
<tr>
<td><strong>Dry mouth</strong></td>
<td>dry mouth hinders absorption of some preparations, eg Actiq</td>
<td>seek specialist advice; advise rinsing the mouth with water before use; alternatives may be less affected (eg sprays) but require retitration</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>in addition to additive effects with other CNS depressants, breakdown of alfentanil and fentanyl is inhibited by CYP 3A4 inhibitors, eg macrolide antibiotics,azole-antifungals, grapefruit juice, some antiretrovirals; thus dose requirements may change if such drugs are initiated or stopped</td>
<td>use alternatives if possible if such medicines cannot be avoided, ask the patient and carers to omit further doses if signs of accumulation occur (eg drowsiness, delirium) and seek advice</td>
</tr>
<tr>
<td><strong>Titrating regular opioids</strong></td>
<td>prescribers will be familiar with titrating regular opioids (eg modified-release morphine preparations) according to prn usage; however, ROOs are titrated separately</td>
<td>consider the background and episodic pains separately; titrate regular opioids to control the former; ROOs manage the latter</td>
</tr>
<tr>
<td><strong>Aberrant use</strong></td>
<td>the risk of aberrant use (eg addiction disorder) may be greater where the opioid plasma levels rise rapidly (eg ROOs and parenteral opioids)(^\text{16}) guard against unintended misuse, eg by children – some may be mistaken for sweets, eg lozenges</td>
<td>clinicians should exercise the same vigilance as with other opioids ROOs should be used with additional caution in patients at higher risk, eg a history of opioid misuse(^\text{16})</td>
</tr>
<tr>
<td><strong>Adverse effects common to all opioids</strong></td>
<td>morphine, fentanyl and alfentanil are all mu opioid agonists and thus share many adverse effects (eg drowsiness, respiratory depression, nausea, delirium)</td>
<td>if mild but bothersome, reduce dose consider ‘counter-measures’, eg antiemetics for nausea if severe respiratory depression occurs, administer naloxone while awaiting transfer to an acute hospital</td>
</tr>
<tr>
<td><strong>Frequency of use</strong></td>
<td>frequent use may suggest insufficient regular analgesia; further, accumulation may occur, particularly with longer-acting fentanyl preparations</td>
<td>the manufacturers of fentanyl-based ROOs advise review of the regular regimen if more than 4 prn doses are required per day if in doubt, discuss with the initiating specialist to ensure the regimen is optimised</td>
</tr>
</tbody>
</table>

Table 2. Common monitoring issues arising when ROOs are used in the palliation setting “thus the interactions are similar to those of more familiar medicines metabolised by the same hepatic P450 enzyme, eg statins
ROOs need to be familiar with their monitoring issues (see Table 2).

Summary
Episodic pain is common, and can often be successfully managed in primary care with a careful stepwise approach. ROOs represent a more recent option but uncertainties remain about their place, in particular how much faster than morphine they actually are, and whether fentanyl-based ROOs might worsen postdose adverse effects.

Alfentanil spray, an unlicensed alternative, has some theoretical advantages in selected patients, but these remain unproven in RCTs.

An understanding of the specialist options (including ROOs) may assist GPs in making decisions about onwards referral where required. The titration and use of ROOs differ from that of more familiar opioids, and GPs encountering such patients may find Table 2 a useful summary of the prescribing and monitoring issues specific to these medicines.

1. Reduce underlying causes and triggers if possible
   • bony instability, eg orthopaedic surgery, radiotherapy, vertebroplasty, splints
   • painful ulcers, eg treatment of ischaemia
   • movement-induced pain of any cause: reduce the effort of movement, eg occupational therapy and physiotherapy assessment of suitability for walking aids, equipment, etc

2. Optimise regular analgesia for background pain
   • the WHO ladder approach describes the use of regular opioids (eg slow-release morphine sulphate), paracetamol and NSAIDs
   • other nonopioids may be required for specific situations if background pain is incompletely opioid responsive, eg neuropathic, bony, skeletal or smooth muscle spasm pains

3. Look for neuropathic pain and skeletal muscle spasm
   • both:
     – are common causes of both continuous and/or episodic pain
     – can co-exist with bony instability or complicate deeper ulcers and wounds
     – are often opioid poorly responsive
   • examination may reveal sensory changes or other evidence of nerve damage, or tender muscle spasm; treat with neuropathic agents (eg gabapentin, amitriptyline) and/or skeletal muscle relaxants (eg baclofen, benzodiazepines)

4. Give additional analgesia before/during pain episodes
   • if opioid responsive, consider oral morphine 30–60 minutes before triggers, eg moving/dressing changes; be alert for drowsiness or cognitive impairment once the pain subsides
   • nitrous oxide/oxygen (Entonox) if available locally

5. Discuss with a pain or palliative-care specialist
   • options include:
     – interventional analgesia, eg nerve blocks, spinal analgesia
     – ROOs (particularly if pain is opioid responsive but oral opioids were too slow to act or too prolonged (resulting in drowsiness or cognitive impairment)
     – topical opioids for painful ulcers (these may affect wound healing and are thus often reserved for ulcers without prospect of healing)

Table 3. A stepwise approach to the management of episodic pain in palliative care

References
11. Ozbek H. Agri 1998;10:64–7 (abstract only; article in Turkish).

Declaration of interests
Dr Howard is editor of the Palliative Care Formulary and member of: Royal Berkshire Hospital Drugs and Therapeutics Committee, Berkshire West General Practice Medicines Management Group, Berkshire Area Prescribing Committee, and Berkshire West Palliative Care Service Medicines Management Team; Rachel Howard: none to declare.

Dr Howard is consultant in palliative medicine, Berkshire West, and Rachel Howard is lecturer in pharmacy practice, University of Reading