Acute pain management in the opioid-tolerant patient


Summary

The main goals in treating acute pain in opioid-tolerant patients are effective pain relief and prevention of withdrawal symptoms. This article provides an overview of the issues that practitioners need to consider when caring for potential and actual opioid-tolerant patients experiencing acute pain, for example following surgery or injury. It highlights the importance of a multimodal analgesic approach to pain control and the prevention of withdrawal. It defines the terminology used in managing opioid-tolerant patients in order to allay healthcare professionals’ misconceptions.

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Keywords

Drug therapy, pain and pain management, pain: postoperative, self-medication

This is probably the result of a combination of factors, including acceptance of opioids as an appropriate and effective method of controlling chronic pain; the introduction of convenient modes of administration, for example patches; and an ageing population in the UK (Mehta and Langford 2006).

Pain generally becomes more prevalent as the population ages (Helme and Gibson 2001). Increased incidence of chronic disease associated with advancing age is a risk factor for developing acute and chronic pain (Scudds and Østbye 2001). It is estimated that 13% of the UK population have chronic pain (Fricker 2003).

In the UK approximately half of cancer patients who are undergoing active therapy and more than two thirds of patients with advanced disease experience significant pain (Portenoy and Lesage 1999). From 2006 to 2007 it was estimated that there were 328,767 recreational users of opioids in England (Hay et al 2008).

The evidence for the management of opioid-tolerant patients is limited and therefore recommendations are derived from case reports, personal experience, expert opinion, reviews and retrospective studies (Rapp et al 1995, Lewis and Williams 2005, Mehta and Langford 2006, Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (ANZCA) 2010).

Lewis and Williams (2005) suggested that patients who have been on high doses of weak opioids or strong opioids for more than two weeks may be at risk of opioid tolerance, physical dependence and physical withdrawal. The consensus of opinion in the literature is that opioid-tolerant patients require larger opioid doses and longer periods of post-operative analgesia than patients who have had no recent exposure to opioids (opioid naive) and...
that regular opioids should be continued as a baseline, with additional analgesia provided as required (Lewis and Williams 2005, Mehta and Langford 2006, British Pain Society et al 2007, ANZCA 2010).

Mitra and Sinatra (2004) proposed that the first step in managing pain in the opioid-tolerant patient is to recognise and assess such patients and formulate peri-operative and post-operative management plans designed to provide sufficient pain relief. Mitra and Sinatra (2004) argued that it does not matter if the patient’s tolerance results from legally prescribed or illegally obtained opioids as both cause diminished responses to post-operative opioid doses.

Identification of opioid-tolerant patients in practice

There are three main groups of opioid-tolerant patients (ANZCA 2010):

- Patients who have cancer pain.
- Patients who have chronic non-cancer pain.
- Patients who have a current addiction to opioid or recreational drugs, or those with a previous addiction who are on a maintenance drug programme.

Opioid-tolerant patients are often at risk of their pain being underestimated and undertreated (Mehta and Langford 2006). This can result from doctor or nurse bias and ignorance, or fear of opioid addiction, which may be exhibited by healthcare professionals and patients alike. Patients who take recreational drugs and other substances are not always open about the types and doses they use. This increases the difficulty of estimating the therapeutic opioid dose.

Useful terminology

Important terminology related to tolerance and addiction is listed and discussed here to assist healthcare professionals in managing pain control for opioid-tolerant patients.

Opioid

Opioid is a broad term used to include naturally occurring, synthetic and semi-synthetic medicines that act like morphine.

Examples of strong opioid analgesics include:

- Morphine sulphate.
- Methadone.
- Fentanyl.
- Buprenorphine.
- Oxycodone.

Weak opioids include codeine and tramadol.

Tolerance

Tolerance associated with opioid exposure means that patients require increased amounts of the drug to maintain the original pharmacological effects (Mitra and Sinatra 2004). Long-term opioid exposure results in neuroadaptive changes that include opioid receptor desensitisation and a decrease in the number of available opioid receptors (down-regulation).

Another feature of tolerance is up-regulation of the cyclic adenosine monophosphate pathway. Normally opioids inhibit this pathway, but with long-term exposure to them the pathway recovers, resulting in tolerance (Mitra and Sinatra 2004).

The effect of these phenomena is increased pain transmission and magnified responses to pain. The practical significance of tolerance in acute pain management is that patients who have had previous exposure to opioids require higher opioid doses following surgery or injury than opioid-naïve patients.

Addiction

Addiction is ‘a chronic disorder, characterised by the compulsive use of a substance, which results in physical, psychological or social harm to the user and continued compulsive use despite that harm’ (Rinaldi et al 1988). Opioids may be used recreationally, for their psychological and physical effects, rather than clinically for pain relief.

Pseudo-addiction

This refers to behavioural changes similar to those exhibited by patients with opioid dependence or addiction that occur as a result of inadequate analgesia. In pseudo-addiction, patients may exhibit aberrant drug-taking behaviour indicative of true addiction, for example ‘clock watching’ or demanding pain relief, which diminishes once adequate pain control is achieved (Weissman and Haddox 1989).

Physical dependence

This is an expected state that develops as a physiological adaptation to repeated use of a drug. It is characterised by physical withdrawal syndrome if the drug is stopped abruptly. In acute pain management, physical dependence can be presumed to have occurred if opioids are given regularly, even over a period as minimal as one to two weeks (Lewis and Williams 2005). Gradual reduction of the dose will prevent the occurrence of withdrawal syndrome.

Physical withdrawal

This syndrome occurs if an opioid is abruptly stopped, rapidly reduced or reversed by administration of an antagonist such as naloxone. The syndrome results in unpleasant and unwanted side effects (Collett 1998, ANZCA 2010).
The presence of withdrawal is not necessarily indicative of addiction, as patients exhibiting withdrawal may be physically, but not psychologically, opioid-dependent. The signs and symptoms of withdrawal are listed in Box 1.

**Acute pain management**

It is important that an acute pain management plan is identified for opioid-tolerant patients when they undergo surgery or experience an acute pain episode. The plan should include the following goals (Lewis and Williams 2005, Mehta and Langford 2006):

- Identification of those patients at risk of opioid tolerance.
- Effective pain control.
- Avoidance of withdrawal symptoms.
- Avoidance of overdose.
- Treatment of psychological disorders such as anxiety.
- Patient acceptance of a suitable maintenance opioid regimen.

To achieve these aims an open and honest approach is required by the patient and staff members. This approach should involve the pain service and an anaesthetist to formalise an appropriate pain management plan (Box 2). If patients are on a drug-maintenance programme, confirmation of their medication and doses from their drug-dependency unit should be obtained. Patients are not always open or honest regarding the amount or type of opioids they are taking. If opioids are prescribed outside of the patient’s normal regimen, it may affect pain relief and have adverse effects, including withdrawal. It is important to ask patients about any supplementary or unauthorised opioids they may be taking, as this will affect their requirements.

**Pain management techniques**

Three reviews (Mitra and Sinatra 2004, Lewis and Williams 2005, Mehta and Langford 2006) and one case report (Rapp et al 1995) agree that opioid-tolerant patients require larger doses of opioid post-operatively than patients who are opioid naive and that pre-existing opioid regimens should be continued with additional analgesia provided as required. If patients are unable to tolerate their normal regimen then the pre-existing opioid should be omitted and substituted with alternative analgesia, such as patient-controlled analgesia (PCA) (Mitra and Sinatra 2004, Lewis and Williams 2005, British Pain Society et al 2007, ANZCA 2010). The surgery may alter the nature of the pain or even alleviate the pain (Lewis and Williams 2005). Opioid transdermal patches and oral opioids should be stopped before major surgery to avoid post-operative problems associated with delayed opioid absorption and inflexible dose delivery. This may be due to changes in gastrointestinal function post-operatively, for example ileus or vomiting. Opioid patches deliver prolonged analgesia. This makes dose titration difficult as it will take at least 12 hours to monitor effectiveness. Short-acting opioids are more appropriate for acute pain management because of their quick onset of action (Mehta and Langford 2006).

PCA is the advised modality, used alone or in addition to epidural or regional techniques such as tissue infiltration or nerve blockade with local anaesthetics. The intravenous route used for PCA allows for 100% bioavailability – the

**BOX 1**

**Signs and symptoms of opioid withdrawal**

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Sweating</td>
<td>Restlessness</td>
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<tr>
<td>Papillary dilation</td>
<td>Irritability</td>
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<tr>
<td>Tachycardia</td>
<td>Nausea</td>
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<tr>
<td>Hypertension</td>
<td>Abdominal cramps</td>
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<tr>
<td>Vomiting</td>
<td>Increased sensitivity to pain</td>
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<tr>
<td>Diarrhoea</td>
<td>Myalgia (muscle pain)</td>
</tr>
<tr>
<td>Yawning</td>
<td>Dysphoria (opposite to euphoria)</td>
</tr>
<tr>
<td>Fever/chills</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Lacrimation (secretion of tears)</td>
<td>Crying for opioids</td>
</tr>
<tr>
<td>Piloerection (erection of the hair of the skin)</td>
<td>(Adapted from Collett 1998)</td>
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</tbody>
</table>

**BOX 2**

**Goals of acute pain management in opioid-tolerant patients**

- Identify the at-risk population – patients on long-term opioids for cancer or chronic non-cancer pain, drug abusers, recovering drug misusers on maintenance programmes.
- Prevention of withdrawal symptoms and complications.
- Effective analgesic treatment in the acute pain phase.
- Involvement of multidisciplinary and/or specialist teams for treatment of psychological disorders if needed.
- Management of aberrant drug-taking behaviours, for example unapproved use of other drugs, hoarding of drugs or altering drug prescriptions.
- Rehabilitation to suitable maintenance opioid therapy.

(Adapted from Macintyre and Schug 2007)
amount of a given drug that is absorbed and reaches the system (Rang et al 2007) – and a rapid onset of analgesia. This is especially important in the initial post-operative period when oral administration of opioids may have unpredictable results due to impaired absorption in the stomach (Bennett and Brown 2003).

Opioid transdermal patches may also have unpredictable absorption rates in the post-operative period because of the particular pharmacokinetics, for example the presence of oedema and fever (Fallon 2003). The term pharmacokinetics can be defined as what the body does to the drug, as opposed to the word pharmacodynamics, which can defined as what the drug does to the body.

The PCA dose should be converted to account for the difference between oral dose and intravenous dose requirements. The intravenous dose is adjusted downwards from the oral dose because intravenous administration bypasses gastrointestinal absorption variables and first-pass metabolism. This term means that an oral dose is metabolised efficiently by the liver so that the amount of drug that reaches the systemic circulation is significantly less than the amount absorbed, causing low bioavailability (Rang et al 2007).

PCA, together with a background infusion, is advised to maintain the baseline opioid requirement (Mitra and Sinatra 2004, Lewis and Williams 2005). Lewis and Williams (2005) claimed that current evidence suggests only 50% of the baseline opioid requirement is required to prevent withdrawal symptoms. To use PCA effectively, they advised converting the oral 24-hour opioid dose to an intravenous dose and then running between 50% and 100% of this calculated dose as a background infusion over 24 hours. It is recommended that the starting bolus dose is increased to 1.5-2.0mg in the opioid-tolerant patient as opposed to the 1mg standard bolus dose used in opioid-naive patients.

Box 3 illustrates a suggested PCA regimen for a patient who presents for surgery while taking oral, long-acting morphine sulphate (30mg twice daily) plus short-acting oral morphine solution 10mg twice a day.

Once the patient is able to resume an oral analgesic regimen, the PCA opioid dose can be converted back to its equivalent oral dose. This will reflect the individual patient’s requirements and the GP will need to be informed of any changes to the previous opioid regimen.

Epidural administration alone, even if it contains an opioid, will not prevent opioid withdrawal symptoms (Mitra and Sinatra 2004, British Pain Society et al 2007). A PCA with a background infusion can be used with an epidural, in addition to the local anaesthetic epidural, to address the opioid tolerance.

The literature advocates, where possible, the use of multimodal analgesia, for example paracetamol, non-steroidal anti-inflammatory drugs, ketamine and regional anaesthesia, in addition to opioids to improve pain control and to enhance opioid effectiveness (Mitra and Sinatra 2004, Lewis and Williams 2005, Mehta and Langford 2006). There is a wealth of research to support the use of multimodal analgesia for its opioid-sparing properties (Perttunen et al 1999, Remy et al 2005).

There are occasions when acute pain remains uncontrolled in opioid-tolerant patients despite the use of high-dose opioid analgesia regimens. In these patients an N-methyl-D-aspartate (NMDA) receptor, which is located in the dorsal horn of the spinal cord, may have become active. This receptor is usually inactive, but its activation is associated with the development of persistent pain (Dickenson 1997, Woolf and Mannion 1999).

NMDA receptor antagonists, such as ketamine, may be used to block this receptor and return the receptor to its resting state. Evidence suggests that activated NMDA receptors are involved in many types of persistent pain, including post-operative and neuropathic pain (Dickenson 1997, Woolf and Mannion 1999).

Ketamine can also be used as an adjunct to opioids in opioid-tolerant patients to improve pain relief, prevent and improve neuropathic pain, and reduce opioid requirements and opioid-induced side effects (Mitra and Sinatra 2004, Mehta and Langford 2006, Visser and Schug 2006). Ketamine can be administered intravenously as a low-dose infusion for those unable to tolerate oral regimens.
Conclusion

Pain management in opioid-tolerant patients is often complex and challenging. The main goals in treating acute pain for the opioid-tolerant patient are effective pain relief and prevention of withdrawal symptoms. The use of opioids pre-operatively can lead to increased post-operative pain and higher analgesic requirements. To deal with these effectively, management goals need to be set. These should include:

- Identification of opioid-tolerant patients pre-operatively.
- Optimal pain relief. In severe, acute pain, opioid therapy is the mainstay. However, using a multimodal analgesic approach can help to reduce escalating opioid requirements.
- Prevention of withdrawal.

Formulating a plan in collaboration with the patient for re-establishment of previous treatment.

A good understanding of the terminology used in managing opioid-tolerant patients helps allay healthcare professionals’ misconceptions.

Acknowledgement

Each of the articles in this series has been written by a member of the Royal College of Nursing London Pain Interest Group. Nursing Standard would like to thank Felicia Cox, senior nurse, pain management, Royal Brompton and Harefield NHS Foundation Trust, and chair, Royal College of Nursing London Pain Interest Group, for co-ordinating and developing this series.

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International Association for the Study of Pain
www.iasp-pain.org

References


