

Acute pain management for opioid tolerant patients

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INTRODUCTION

Opioid tolerance is usually encountered in specific patients groups:

- Patients who are prescribed long-term opioids for the treatment of either chronic non-cancer pain or for the treatment of cancer pain.
- Patients with a substance abuse disorder with continuing illicit use of opioids, particularly intravenous drug users, or patients who are currently on a maintenance treatment program of either methadone or sublingual buprenorphine.
- There is also emerging evidence that acute opioid tolerance can occur over surprisingly short periods of time in response to intravenous administration of high potency opioids, particularly remifentanyl.

DEFINITIONS

It is essential to have uniform definitions to prevent misconceptions and mislabeling of these groups of patients. It is important that healthcare providers are able to differentiate between the term *addiction* and the normal physiological consequences of remaining on long-term opioids, such as *tolerance* and *physical dependence* (Table 1).

CLASSIFICATION OF OPIOID TOLERANT PATIENTS

Patients with persistent non cancer pain

Epidemiological studies indicate that as many as 11 to 60% of the adult population suffer with chronic pain. The estimates of the prevalence of chronic pain vary widely due to a lack of standardization in the definitions of pain and pain assessment tools. However persistent non-cancer pain is a significant worldwide problem and the use of long-term opioid medication to treat this type of pain is increasing. Patients of this type will be seen in increasing numbers after elective or emergency surgery.

Patients with persistent cancer pain

Opioids are currently the most effective and appropriate treatment for moderate to severe cancer induced pain and remain the mainstay of treatment. Pain is the first symptom of cancer in 25-50% of all cancer patients and up to 75-95% of advanced cancer patients must cope with persistent pain. Cancer pain may be related to disease progression, either local invasion or metastases, or as a consequence of treatments such as surgery, chemotherapy and localized radiotherapy.

Summary

Diagnosis and management of acute pain in opioid tolerant patients is challenging and is often poorly managed in the hospital setting. The evidence base for this group of patients is limited and guidelines are largely based on evidence from case studies, case reports and expert consensus. This article is a review of the current recommendations relating to this group of patients and outlines the approach to management of acute pain in the opioid tolerant patient by anaesthetists in the hospital setting.

Table 1. Definitions related to chronic use of opioids (American Academy of Pain Medicine)

Tolerance	A predictable physiological decrease in the effect of a drug over time so that a progressive increase in the amount of that drug is required over time.
Physical dependence	A physiological adaptation to a drug whereby abrupt discontinuation or dependence reversal of that drug, or a sudden reduction in its dose, leads to a withdrawal syndrome.
Addiction	A disease that is characterised by aberrant drug seeking behaviour and maladaptive drug taking behaviour that may include cravings, compulsive drug use and loss of control over drug use, despite the risk of physical, social and psychological harm. Unlike tolerance and physical dependence, addiction is not a predictable effect of a drug.
Pseudoaddiction	Behaviour that may seem inappropriately drug seeking but are the result of under treatment and resolve when pain relief is adequate.

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Patients with a substance abuse disorder

These patients fall into 3 distinct subgroups:

Active

These are patients who are currently abusing prescribed or non-prescribed opioid medication. The prevalence of heroin use in the UK is 1%. Similar prevalence levels for heroin use have been documented in both the USA and Australia. Intravenous drug abusers are more likely to present with certain types of acute pain, including traumatic injury, limb ischaemia due to inadvertent intra-arterial injection and infections (epidural abscess and infections around injection sites).

The data on the prevalence of addiction in patients taking prescribed opioids for chronic non-cancer pain is limited, suggesting a ranging between 0-50%. Results from these studies should be interpreted with caution as study populations are not consistent with respect to diagnosis and previous history. Prevalence rates also vary depending on the criteria used to define addiction.

Replacement therapy

Opioid maintenance therapy is increasingly recognized to be an effective management strategy for opioid addiction, with oral methadone the most commonly used drug. The methadone maintenance program is effective in reducing injecting behaviour, illicit drug use, criminal activity and the cost to society.

High dose sublingual buprenorphine is increasingly used as a maintenance therapy in opioid addiction, as it is perceived to have less adverse effects and less social stigma than methadone. Buprenorphine is a partial opioid agonist and thus antagonises the effects of additional illicit or therapeutic opioids that are taken. It has a high opioid receptor affinity and supplemental opioids when given in standard doses do not displace it from the opioid receptors, making it ideal for use as a maintenance therapy. However when administered in high doses as part of the maintenance program it can make acute pain management of patients with conventional doses of opioids very difficult. Management of this group of patients will be discussed in detail later.

Recovery

Patients who are now opioid free and in recovery are often concerned that if they are prescribed opioids to manage their acute pain they will run the risk of relapsing back into their previous opioid abuse disorder. Patients should be reassured that the risk of reverting to an active addiction disorder is small and paradoxically ineffective analgesia in this group of patients is more likely to lead to a relapse.

Patients with acute opioid tolerance

There is emerging evidence that acute opioid tolerance or opioid induced hyperalgesia (OIH) could potentially develop over a very short period of time. OIH is a process that has been shown to occur where the administration of opioids can activate pronociceptive mechanisms in the central nervous system, resulting in an actual increase in pain sensitivity. Paradoxically reducing the dose of opioids can help to improve pain management. This process has been demonstrated to occur with patients on long-term opioids particularly patients on a methadone maintenance program. Opioid tolerance and OIH have also been associated with the short term use of high potency opioids, for example remifentanyl, used intraoperatively or as part of the sedation regime in the intensive care

unit. However this association has not been fully established as the studies on this issue have conflicting results.

OPIOID TOLERANT PATIENTS IN THE ACUTE SETTING

Increased workload

Compared with matched opioid naive patients these patients create a greater workload for healthcare professionals and the acute pain team. They require more frequent reviews, more frequent changes to their prescription chart. Patient controlled analgesic (PCA) regimes may require more attention, with increased bolus dose and background infusion rates.

Increased opioid consumption

For a given procedure, postoperative PCA opioid use has been shown to be 2-3 times higher in opioid tolerant patients compared with opioid naive controls.

Increased pain scores

This group of patients consistently report higher pain scores and this can make assessment challenging. It is useful to assess the patients in terms of what they are able to do functionally - their ability to cough, deep breathe, mobilize and complete physiotherapy exercises, as these are likely to be more useful than relying on pain scores.

Consequently, these factors can have a negative impact on the care opioid tolerant patients receive by invoking strong feelings in hospital staff, with patients perceived as 'manipulative' and 'non-cooperative'. Staff who are unfamiliar with such patients may also show apprehension about prescribing large doses of opioid medication that they are unfamiliar with, for fear of causing harm or exacerbating addiction. This may lead to under treatment of pain, an increased level of opioid seeking behaviour by the patient and may ultimately perpetuate an increasing spiral of mistrust in the patient-clinician interaction.

AIMS OF ACUTE PAIN MANAGEMENT

It is important to adhere to a clear and well documented acute pain management plan that both the healthcare staff and patient are aware of. The aims of pain management are categorised as follows:

The provision of effective analgesia

A multimodal approach is always recommended. The provision of effective analgesia needs to incorporate a plan to manage the patient's opioids so that their usual background opioid dose is continued to prevent a withdrawal syndrome, with additional short-acting opioids given for the acute pain treatment (discussed in detail next section). It is also important to use opioid sparing techniques such as:

- Paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors should be prescribed regularly unless contraindicated.
- Local anaesthetic techniques should be employed where possible. Catheter based techniques allow the continuous infusion of local anaesthetic in the postoperative period, decreasing the requirement for additional short-acting opioids.
- Ketamine in low (sub-anaesthetic) doses acts primarily as a non-competitive antagonist of NMDA receptors. Postoperative administration of ketamine in opioid tolerant patients can lead

to improved pain scores and decreased opioid consumption. Often this is administered postoperatively as a continuous low dose IV or SC infusion.

A regime for low-dose intravenous ketamine

Make up 200mg ketamine and 5mg midazolam to 50ml in 0.9% saline and infuse at 2ml.h⁻¹

- Gabapentinoids (gabapentin and pregabalin) are calcium channel modulators that have an established role in the treatment of neuropathic pain. A number of meta-analyses on non-opioid tolerant patients have shown that perioperative gabapentinoids lead to improved analgesia and reduced postoperative opioid consumption, but can also lead to increased sedation scores when compared to placebo. There may be a useful role for these drugs in opioid tolerant patients.

Prevention of withdrawal

All opioid tolerant patients run the risk of developing withdrawal symptoms (Table 2) if their normal dose of opioid is stopped, the dose reduced too quickly or the effect of the opioid is reversed by use of an antagonist such as naloxone. This is not a sign that they are addicted to opioids but is a normal and expected physiological response to physical dependence, which occurs in all patients on long term opioids.

Each patient's usual opioid requirements must be considered, and continued to prevent withdrawal, whilst the additional short-acting opioids are used to manage the acute pain.

Table 2. Symptoms and signs of opioid withdrawal

Sweating
Feeling hot and cold
Dilated pupils
Anorexia
Abdominal cramps
Nausea and vomiting
Diarrhoea
Insomnia
Tachycardia and hypertension
Muscular aches and pains

Continuing dose of usual opioid to prevent withdrawal

It is important to continue a patient's usual dose of opioid perioperatively. If the patient normally takes oral medication but is now nil by mouth, then an equivalent parenteral replacement will be needed (see Example 1).

If the patient's normal opioid requirements are via transdermal patches (fentanyl or buprenorphine), we recommended that these patches be continued.

Buprenorphine is a partial agonist and there is a theoretical risk that it might antagonise full opioid agonists, making acute pain management more difficult. However use of buprenorphine transdermal patches

up to 70mcg.h⁻¹ is unlikely to interfere with the use of full-agonist opioids for acute pain.

Additional opioid for acute pain

For minor procedures short-acting opioids can be administered as required. A starting dose of one sixth of the patient's usual total 24 hour opioid dose, given up to 4 hourly, is recommended.

The use of intravenous PCA is widely recommended as the treatment of choice for administering short-acting opioids for acute pain management as it allows individual dose titration and reduces workload for staff. Often patients require increased bolus doses and may require a background infusion of opioid if unable to take their usual oral opioid. It can be difficult to know the optimal starting dose. One method is to base the size of the bolus on the patient's normal 24 hour opioid requirement (Example 1).

Example 1

An opioid tolerant patient, who normally takes 150mg sustained release morphine twice a day was admitted requiring an emergency laparotomy and will be nil by mouth postoperatively.

- To prevent withdrawal the usual oral 24 hour opioid dose needs to be maintained, i.e. 300mg morphine.
- As he is nil by mouth this needs to be converted to an IV dose.
- Conversion ratio for oral morphine:IV morphine is 3:1 (see Table 3).
- Total IV dose over 24hrs =100mg, i.e a background infusion of 4mg.h⁻¹.
- The bolus dose should be started at 50% of the dose of the background infusion (2mg), with a standard lock-out time of 5mins.

Note that this PCA dose strategy is a guideline and may not be suitable for all patients in all situations. Opioid tolerant patients require more frequent assessments on the ward and it is likely that the initial PCA prescription will need to be altered depending on the patient's response.

Opioid rotation

This technique, where a patient is changed from one opioid to another, is often used in the treatment of both chronic non-cancer pain and cancer pain. This technique is used when patients are gaining tolerance to the analgesic effect of the initial opioid and, the effective dose required is increasing. However we know that patients gain tolerance to both the beneficial effects of opioids (e.g. analgesia) and also to side effects (e.g. constipation and sedation), but the rates at which tolerance develops is not uniform. So if a patient develops tolerance to the analgesic effects of the opioids at a greater rate than they develop tolerance to undesired effect, they are often unable to tolerate the increased dose needed for analgesia due to excessive side effects.

In this scenario rotating to a different opioid can lead to reduced side effects and improvement in pain relief. The concept is based on the rationale that different opioids do not act to the same degree on the various opioid receptors, they are often metabolized differently and there is incomplete cross-tolerance between different types of opioids.

When conducting an opioid rotation, it is recommended to calculate opioid consumption in the previous 24 hours in morphine equivalents and then reduce this dose by 30-50% to allow for incomplete cross-tolerance among the different opioids (Example 2).

Example 2

A patient on a methadone maintenance program taking 100mg daily, requires a major surgical intervention for which he will be nil by mouth postoperatively.

He is unable to take oral methadone, so we need to convert his dose of methadone to a suitable dose of IV opioid to prevent withdrawal.

- Need to convert his last 24hrs dose of methadone to oral morphine equivalents:
 - Oral methadone:oral morphine is 1:2 or 1:3 (see Table 3)
- Using 1:3 ratio 100mg oral methadone is equivalent to 300mg of oral morphine.
- 300mg oral morphine is equivalent to 100mg IV morphine
- As there is incomplete cross tolerance between the different types of opioids we reduce the equianalgesic dose of oral morphine by 50%.
- Dose of IV morphine required over 24hours to prevent withdrawal is 50mg
- So PCA should have morphine at 2mg.h⁻¹ background infusion and starting bolus dose at 50% of the background infusion - 1mg bolus.

Multidisciplinary team approach

It is beneficial to have a collaborative approach with other hospital specialities, such as drug and alcohol services, palliative care and psychology. Regular review by the different specialities within the team provides a more holistic service and helps to identify and deliver the pain management requirements of the patient throughout their in-patient stay. Close liaison with the patient's general practitioner is also necessary to continue the management in the community setting.

Step-down analgesia plan

It is important to have a plan on how to convert the patient back from IV opioids to oral. It is recommended to calculate the patient's last 24 hour consumption of IV opioids and convert this back to the oral equivalent. Then administer 50% of this dose in a sustained release oral preparation and have immediate release opioids prescribed on as required basis. The dose of the immediate release opioids should be 1/6th of the calculated total 24 hour oral equivalent (Example 3).

Example 3

A patient recovering from major surgery is now able to eat and drink and the plan is to convert him from his IV PCA morphine to oral morphine. He has used 60mg IV morphine in the last 24hrs.

- Need to covert IV morphine dose to oral morphine equivalents:
 - 60mg IV morphine is equivalent to 180mg oral morphine.

- 50% of the calculated oral equivalent dose is given in a sustained release form e.g. 45mg of morphine sulphate sustained release twice daily.
1/6 of the calculated oral equivalent dose is given in the immediate release form on an as required basis e.g. oramorph 30mg up to 4hrly.

It is vital that the patient's general practitioner is made aware of doses of opioids that the patient will be discharged home on and how they should be tapered down.

Management of patients on high dose sublingual buprenorphine

High dose sublingual buprenorphine is being increasingly used as a maintenance therapy in opioid addiction, as it is perceived to have less adverse effects and social stigma. It is typically used in doses ranging from 8-32mg every 2 to 3 days.

Buprenorphine is a partial opioid agonist and its maximum effect at the μ -opioid receptor is less than that of a full agonist producing a ceiling effect for respiratory depression and analgesia. It also has a very high opioid receptor affinity and its binding to opioid receptors is not easily reversed by other opioids. These pharmacological properties make it ideal for use as a maintenance therapy, However

Table 3. *Estimated equianalgesic doses of opioids (Journal of Pain and Symptom Management, 2001)*

Drug	IV dose (mg)	Oral dose (mg)
Morphine	10	30
Oxycodone	10	15 – 20
Fentanyl	0.15 – 0.2	n/a
Methadone	10	10 – 15
Buprenorphine	0.3	0.8 (sublingual)

Table 4. *Comparison of oral morphine and transdermal patch dosage (The British Pain Society, 2007)*

Oral morphine (mg.24h ⁻¹)	Buprenorphine patch (mcg.h ⁻¹)	Fentanyl patch (mcg.h ⁻¹)
10	5	
15	10	
30	20	
45		12
60	35	
90	52.5	25
120	70	
180		50
270		75
360		100

Table 5. Perioperative pain management strategies for patients stabilized on high dose buprenorphine⁴

Minor procedures

- Continue the current buprenorphine regimen (and consider an increase of 25%)
- Maximize non-opioid treatments.

Major procedures

- Continue the usual dose of buprenorphine + 25%
- Maximize non-opioid analgesia
- Consider titration of high dose intravenous opioids such as fentanyl or morphine. Patients should be closely observed for adverse effects of sedation or respiratory depression - HDU care is appropriate where available.

Or

- Cease buprenorphine 72 hours preoperatively and commence a full opioid agonist (methadone or sustained release morphine) 24 hours later, or earlier if opioid withdrawal is noted.
- Additional doses of a full agonist can then be titrated to withdrawal symptoms preoperatively and analgesic requirements postoperatively.

Where:

- buprenorphine <4mg per dose - commence methadone 20mg.day⁻¹ or morphine 60mg.day⁻¹
- buprenorphine >4 mg per dose - commence methadone 40mg.day⁻¹ or morphine 80mg.day⁻¹

they can also make the treatment of acute pain by conventional opioids difficult. Table 5 outlines possible treatment strategies for this group of patients

CONCLUSION

The acute pain management of opioid tolerant patients is often challenging and it is important to use a multimodal approach to analgesia. Appropriate doses of opioid are needed to prevent withdrawal and provide effective analgesia. Be aware of the potential acute pain management problems of high dose sublingual buprenorphine. Note that the dose regimens outlined in this article are suggestions only and may not be suitable for all patients or in all situations.

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