Opioids are the cornerstone therapy for the treatment of moderate to severe pain. Accumulating evidence suggests that opioids may cause opioid-induced hyperalgesia. Somewhat paradoxically, opioid therapy aiming at alleviating pain may render patients more sensitive to pain and potentially may aggravate their pre-existing pain.

Several recent articles have reviewed and highlighted important aspects of opioid-induced hyperalgesia, which reflects the growing interest and rapidly expanding body of literature regarding this phenomenon.\(^1\)\(^-\)\(^5\) The term ‘paradoxical pain’ has been used in the past and associated with the now unfounded theory of morphine-3-glucuronide being antalgic.\(^6\) The term ‘hyperalgesia’ is more informative from both a mechanistic and clinical viewpoint.

An increase in pain to noxious stimuli must have been witnessed at some point by every palliative care professional, albeit this clinical phenomenon will have been interpreted in different ways. An increase in pain to noxious stimuli, or hyperalgesia, can occur in two types of syndrome. The first is part of the triad of opioid toxicity and also includes to variable degrees, hallucinations, vivid dreams, myoclonic jerks, confusion, agitation and drowsiness. The second form of hyperalgesia occurs as an isolated phenomenon in patients who are taking opioid medication and in whom there are none of the classical signs of opioid toxicity. In both situations clinical evidence suggests that opioids can elicit increased sensitivity to noxious stimuli suggesting that the administration of opioids can activate both pain inhibitory and pain facilitatory systems. The exact mechanism of hyperalgesia with opioid toxicity and without opioid toxicity is unclear and may be very different in each of these two broad conditions. There will be a third group of patients in whom the diagnosis of opioid-induced hyperalgesia is missed and escalation of the dose of opioid results in opioid toxicity.

**Opioid hyperalgesia and tolerance to opioids**

Although some of the underlying mechanisms may be similar, it is important to clarify the difference between tolerance and opioid-induced hyperalgesia. Tolerance relates to the desensitization of antinociceptive opioid pathways, with a corresponding right shift in the dose-response curve – this is reflected in a reduction of analgesic effect. In contrast, opioid-induced hyperalgesia is an increase in pain sensitivity with upregulation of pronociceptive pathways. There is a downward shift in the dose-response curve and, perhaps most importantly, increasing opioid doses cause an increase in pain, with loss of analgesic effect.

**Opioid induced hyperalgesia – underlying mechanism**

A range of mechanisms is likely to be involved at all levels of the nociceptive system. There is evidence of changes in the peripheral nerves involved in pain processing, with alteration in intracellular messengers such as protein kinase C. Major changes within the spinal cord include acute receptor desensitization via uncoupling of the receptor from G-proteins, up-regulation of the cAMP pathway, activation of the N-methyl-D-aspartate (NMDA) – receptor system, as well as involvement of spinal prostaglandins and nitric oxide pathways. Alterations within the brain, including the rostroventral medulla and an increase in descending facilitation may also play a role in opioid-induced hyperalgesia.\(^7\)\(^-\)\(^13\) Interestingly, the same mechanisms have been identified in the development of tolerance suggesting that tolerance may result from a pain sensitization process more than from a decrease in the opioid effectiveness. This is however unlikely to be the whole story with tolerance. Numerous reports exist demonstrating that opioid-induced hyperalgesia and tolerance are observed both in animal and human experimental models. In true clinical pain states, as opposed to experimental models, we believe that clinical history and examination will differentiate between the phenomena of opioid-induced hyperalgesia and tolerance.

Clinical opioid-induced hyperalgesia is seen in pain of acute, chronic non-malignant and malignant origin, in addition to pain states in patients with a history of opioid dependence.

The clinical differentiation between opioid-induced hyperalgesia and antinociceptive tolerance is clearly complicated,
however it is perhaps easier to identify in chronic cancer pain than in other clinical situations. We know from longitudinal follow-up that patients with cancer-related pain can remain on the same opioid dose for months or even years and that, on the whole, clinically-relevant opioid tolerance is not a major issue in cancer pain management. However, we do not have any idea of the true incidence of opioid-induced hyperalgesia. There exists a subgroup of patients with cancer who seem to have difficulties with pain control regardless of the underlying pathophysiology. This can exist from early on or can develop later in the illness. Classically, an increase in opioid dose results in worsening pain which is quite different to opioid tolerance where an increase in dose may be ineffective but not associated with hyperalgesia. As such patients are understandably very distressed, the problem can often be mislabelled as general distress. The general hyperalgesia and associated distress may also be labelled naively as ‘total pain’ and of course it is genuine ‘total pain’ according to our modern understanding of the complex underlying mechanisms of this phenomenon, and as such needs appropriate modern palliative care management. Clearly prognosis can be shortened if an appropriate diagnosis is not made, either because the patient is offered ‘palliative sedation’ or is rendered opioid toxic by continuing escalation of opioid medication.

The obvious question is why does this subgroup of patients suffer from opioid-induced hyperalgesia? The suspicion of a genetics link seems plausible. Other factors that may predispose to the development of opioid-induced hyperalgesia include the type of opioid, with greater evidence for the phenanthrenes than other types. Opioid use in high doses or rapidly escalating doses may also be relevant. The evidence for a postulated hyperalgesia, related to activation of excitatory pathways at very low doses is limited in the clinical setting.

Successful strategies that may decrease or prevent opioid-induced hyperalgesia include the concomitant administration of drugs like NMDA-antagonists, alpha2-agonists such as clonidine, or nonsteroidal anti-inflammatory drugs (NSAIDs), opioid switch or combinations of opioids with different receptor selectivity.14,15

It seems that as with most things the starting point should be a question: ‘What is really happening to my patient who despite escalating doses of opioid has worsening pain and in fact generalised pain and distress?’

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