Opioid-induced hyperalgesia (OIH) and its implications for everyday anaesthetic practice

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Introduction
Opioids are a class of drugs well known to the modern anaesthetist. Etymologically, the world opium originates from the ancient civilisation of Macedonia. Opi means drunken and um is the word for mind. Our modern “opioid” drugs therefore have chemical and effectual similarity to opium.

Opioid use in clinical practice holds a familiar peril encompassing tolerance and dependency. Recently, new studies have led to the discernment of another potential treatment ramification: the paradoxical phenomenon of “opioid-induced hyperalgesia (OIH)”. Initially, it is easy to mistake OIH for an alternative perspective on tolerance; if the same treatment endpoint is used: both phenomena will apparently necessitate an eventual increase in the required opioid dose. The purpose of this article is to clearly define opioid-induced hyperalgesia as a separate entity, to discuss its underlying physiological mechanisms and to point out the known modalities in its treatment and prevention.

Methods
There have been several recent reports on opioid-induced hyperalgesia. A Medline® search was done using the keywords “opioid”, “hyperalgesia” and “induced”. Access to full-text articles was obtained through the library server of the University of the Free State. A separate manual search of leading anaesthetic journals was carried out to identify articles that might have been missed by the online electronic search. Articles explaining the key points of OIH were then selected as the foundation to explain the concepts of this discussion.

Results
How do we even know that such an abstract condition exists? A recurring concept in the reviewed literature deals with the evidence that opioid-addicted subjects differ in their baseline pain sensitivity to cold pressor stimulation. Several follow-up studies confirmed that the hyperalgesic response in methadone-maintained patients is also dependent on the pain modality (heat, chemical, cold, etc.), with the cold pressor pain response more prominent than electrical stimulation, for instance. From this evidence it is possible to hypothesise that hyperalgesia develops differentially for different pain types.

Celerier et al. proposed on the basis of their work in animal studies that the whole nociceptive pathway is upregulated to a higher level with chronic opioid exposure. The pronociceptive pathway becomes sensitised (opioid-induced hyperalgesia) and, as a compensatory response, the opioid-dependent antinociceptive pathways are upregulated as counterbalance, establishing a whole new equilibrium in a high potential energy state. This “high level” of equilibrium is presumably prone to aberrations, and this leads to vulnerability in the pain control pathways. This neuronal hyperactivity might become unmasked by further opioid treatment or by withdrawal, which manifests as hyperalgesia.

Another commonly cited phenomenon is that of hyperalgesia observed after the withdrawal of remifentanil infusion, especially pertaining to hyperesthesia in the areas surrounding the surgical incision wound. Several laboratory studies point to the development of hyperalgesia as a result of hind paw incision in animals after a prolonged period of morphine injections. This finding correlates well with human studies, which show that patients receiving a high versus a low intraoperative opioid dose have higher postoperative opioid requirements.

Several mechanisms underlying opioid-induced hyperalgesia have been proposed. Most often cited is deranged excitatory amino acid (EAA) activation and metabolism, especially that of glutamate through the NMDA receptor with phosphokinase C (PKC) cascades, which leads to the modulation of cellular function. It appears that the cellular sites of tolerance and hyperalgesia may be communal at the level of excitatory amino acid (EAA) receptors. The exact mechanism whereby opioids activate EAAs is currently unknown.

Discussion
In order to understand the importance of opioid-induced hyperalgesia and to clearly differentiate OIH from pharmacological tolerance, it is necessary to make a clear distinction between the underlying mechanisms. This is of particular importance, since tolerance would require dose escalation, whereas OIH would require dose reduction. Pharmacological tolerance leads to a desensitisation of the normal opioid antinociceptive effects. In contrast to this is the active sensitisation (by opioid) of the pronociceptive processes. Both lead to the same clinical conclusion: the patient may need ‘more’ analgesia.

It is increasingly being realised that neuroplasticity plays an important...
role in the modulation of the pain system. In other words, the nociceptive pathways are not ‘hot-wired’, but responsiveness adjusts according to circumstances. Modulation of the pain system is mostly a result of phosphorylation of the receptor and ion channels and their regulatory proteins. Opioid-induced hyperalgesia fits this paradigm in that it sensitises the neuroplastic process. Central to its modulating function are the NMDA receptors, with their intracellular sequelae, mainly the calcium-dependent activity of phosphokinase C.

How does this influence anaesthetic practice? Recently published data shows that perioperative pain therapy is still suboptimal, and taking extra care in preventing nociceptive sensitisation by opioids may bring us closer to the stated goals of perioperative pain relief (less than 5% with severe perioperative pain).

Currently, the only concrete evidence for the use of ketamine comes from studies which show advantages in preventing postoperative hyper-sensitivity with remifentanil infusions. Greater understanding of this condition will lead the informed anaesthetist to consider alternative therapies for treating postoperative pain, such as multimodal drug regimes incorporating NSAID drugs, ketamine and regional anaesthesia, instead of relying on opioid drugs alone. In addition, the informed physician will consider opioid-induced hyperalgesia as a possible cause for the perioperatively increased analgesia requirement, with subsequent lowering of opioid dosing. A future research field clearly will include further clinical studies on the prevention of development of opioid-induced hyperalgesia. 

References
1. “Opiate”, from Wikipedia.
6. Angst MS, Koppert W, Pahl I, Clark DJ, Semelz M. Short-term infusion of remifentanil in humans causes hyperalgesia during withdrawal.