INVITED COMMENTARY

Role of anaesthetics and opioids in perioperative hyperalgesia
One step towards familiarisation

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Opioids produce analgesia. Nevertheless, clinical experience indicates that they may result in increased pain sensitivity, or, opioid-induced hyperalgesia. The development of opioid-induced hyperalgesia may involve an interaction between neuropharmacological facilitation and inhibition of pain, an abnormal neuroplasticity of the μ opioid receptor system, an as yet unclear dysfunctional cellular recruitment within the brain and spinal cord centres, and sensitisation of pronociceptive pathways. Each or all of the above contribute to the establishment of a condition wherein pain appreciation is heightened despite the administration of opioids in appropriate doses and regimens.

Our understanding of the causes and conditions that permit the development of perioperative opioid-induced hyperalgesia, and the drugs or settings that might prevent its occurrence are limited, as most information is derived from volunteer studies. Our knowledge of the sequence of opioid-induced hyperalgesia events in animals is also limited. Those existing emerge from various facets of protocols that are seldom relevant to clinical practice. As a result, anaesthesiologists still work lacking both an understanding of the basic scientific foundation and a clinically relevant interpretation of opioid-induced hyperalgesia.

Two drugs have become cornerstones of general anaesthesia during recent decades: remifentanil and sevoflurane. The former has become a major component of many intraoperative and postoperative intravenous (i.v.) anaesthesia and analgesia protocols. Sevoflurane is used ubiquitously for maintenance and even induction of general anaesthesia, inside and outside the operating room. Alas, the enthusiastic uptake of these two agents has unveiled part of their dark side: they may trigger opioid-induced hyperalgesia during their postadministration phase. Data show that the more intraoperative remifentanil given, the more intense is the postoperative secondary hyperalgesia, and the higher are the doses of morphine necessary to control pain adequately. Sevoflurane has not been proven to interfere directly with pain, rather it is associated with emergence agitation. But it remains uncertain whether the agitation conceals a lack of adequate analgesia, one more reason why relevant physiological and pharmacological data are hard to obtain in humans. Animals remain the main source of detailed data within the puzzle of pain regulation.

From a clinical standpoint, morphine and remifentanil are the drugs to which opioid-induced hyperalgesia has been mostly attributed, mainly due to their abundant postoperative use. Little basic and clinical data exist with regard to other opioids, such as methadone and buprenorphine that may be used as alternatives in multidisciplinary modes. In addition, studies of postoperative opioid-induced hyperalgesia have been too short to ascertain the duration of the phenomenon, with the exception of a study in mice following a single remifentanil dose. If these findings were to be adopted into clinical practice, then the antinoceptive armamentarium would become narrower, with the result that our patients’ much deserved pain control might become unachievable. Although this is disappointing, the situation is made worse when considering that...
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opioids are used daily in conjunction with inhalation anaesthetics, mainly sevoflurane, to reduce the minimum alveolar concentration (MAC), but with the effect of later inducing a hyperalgesic state. A study reported in this issue of the European Journal of Anaesthesiology, using a single structured animal model, seems to tackle most of the issues raised. Abreu et al. explored factors that relate to the following clinical questions: Would various opioids in clinical use affect sevoflurane requirements, as does remifentanil? Would they subsequently cause opioid-induced hyperalgesia? Would these effects last longer than several hours? and What is the role of N-methyl-D-aspartate (NMDA) receptor activity in the process of opioid-induced hyperalgesia? The last question relates to the accepted theory that the central glutaminergic system plays a key part in the way that neurological mechanisms interact between pain and analgesia. Activation of NMDA receptors and inhibition of central systems engage intimate connections with the glutamate transporter system. Ketamine, an NMDA antagonist, has a possible role in hyperalgesia. Abreu et al. hoped to underscore the NMDA receptors’ regulating function in this matter, assuming that they play a part in the underlying processes of opioid-induced hyperalgesia, this time associated with both opioids and inhalational anaesthetics.

This study is characterised by a precisely gauged sevoflurane MAC based on two rat models: one that controlled somatic (clamping) and behavioural responses (Von Frey and Randall-Selitto tests) to pain, and another that was below the effective ones. Although previously employed, these methodologies applied to the same animal are intended to assess the effects of opioids on both MAC values and pain response. This study is the first of its kind to show precise drug interactions together with the subsequent advent of opioid-induced hyperalgesia. A reduction in the withdrawal thresholds of the tests indicated the development of opioid-induced hyperalgesia. Buprenorphine, methadone and morphine were also tested by the intraperitoneal route, while remifentanil was infused for 2h. The duration of the effect of the drugs on hyperalgesia and MAC were determined over the course of one month. A physiological saline control group was also studied. The remifentanil-treated rats were in the group subjected to ketamine coadministration, aiming at assessing its antihyperalgesic effects.

The results of the study confirmed long-lasting clinical suspicions, that sevoflurane MAC is reduced by remifentanil immediately following its administration; however, interestingly, it induces an increase observable 24h later. This delayed increase could be a feature of opioid-induced hyperalgesia, as these features and the detected decrease in mechanical thresholds were blocked when ketamine was coadministered. The MAC increase lasted up to 3 weeks following remifentanil administration. Buprenorphine, methadone and morphine produced phenomena similar to those generated by remifentanil; however, they were only followed-up for 1 week.

What do these findings mean for clinical practice? They strengthen the clinical truism that various opioids, notably morphine and remifentanil, can decrease sevoflurane requirements soon after their administration. At a later time, this situation reverses, signifying the establishment of hyperalgesia. At the same time, the efficacy of the opioids remains unaltered. Importantly, ketamine proves useful in this context, as it inhibits the NMDA receptors. Consequently these are engineered to prevent or inhibit the advent of sevoflurane MAC and opioid induced hyperalgesia.

Does the knowledge attained from the current study advance clinical pain insight and analgesia management to a higher level? Unfortunately, clinical protocols may not change, and hyperalgesia will still occur until we have acquired clinical confirmation of the reported findings from animal studies, evidence regarding the role of other inhalation anaesthetics in the induction of opioid-induced hyperalgesia, and indications as to whether other opioids, such as fentanyl, also have the potential to produce opioid-induced hyperalgesia with a similar duration as remifentanil.

Acknowledgements relating to this article

Assistance with the commentary: none.

Financial support and sponsorship: none.

Conflicts of interest: none.

Comment from the editor: this invited commentary was checked and accepted by the editors but was not sent for external peer review.

References

1 Angst MS, Clark JD. Opioid-induced hyperalgesia. A qualitative systematic review. Anesthesiology 2006; 104:570–587.