BJA
British Journal of Anaesthesia

Volume 105, Number 5, November 2010

British Journal of Anaesthesia **105** (5): 555–7 (2010)
doi:10.1093/bja/aeq286

EDITORIAL

Opioid-induced hyperalgesia: pain hurts?

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In the current issue of the *British Journal of Anaesthesia*, Shin and colleagues[1] report that propofol used for the maintenance of general anaesthesia may prevent remifentanil-induced hyperalgesia. In their study, a comparison of propofol and sevoflurane combined with either high dose or low dose of remifentanil for the maintenance of general anaesthesia in breast cancer surgery was conducted. They showed that remifentanil hyperalgesia was induced only by a high dose of remifentanil during sevoflurane anaesthesia but not in propofol anaesthesia. Furthermore, propofol and high-dose remifentanil-based anaesthesia provided better postoperative analgesia compared with sevoflurane and high-dose remifentanil. This is an interesting finding which provides further evidence that the use of high doses of remifentanil intraoperatively may elevate postoperative pain scores, and subsequently increase the opioid requirements and the occurrence of their adverse effects in patients. From a clinical perspective, this study indicates that the use of high-dose remifentanil for lengthy procedures may best be avoided, as patients' postoperative comfort could be compromised. Although total postoperative opioid use was meticulously monitored, it remains unclear what the number and the duration of intense pain periods (VAS$>$7) were. Intense pain sets off a cascade of neuronal events, but relationship of these with the development of chronic pain remains unclear. The study also raises the question whether the increased pain scores and increased demand for opioids observed after operation could be associated with remifentanil-induced hyperalgesia, with remifentanil-induced tolerance, or with both.

The International Association of the Study of Pain (IASP) defines hyperalgesia as 'an increased response to a stimulus which is normally painful'. Therefore, the increased perception of pain after remifentanil-based anaesthesia could be associated with opioid-induced hyperalgesia. In contrast, it is well established that chronic opioid therapy is associated with the development of tolerance which refers to 'a decrease in susceptibility to the effects of opioid due to its continued administration'. The potential of opioids to induce acute tolerance after short-term administration during anaesthesia in surgery has not been fully established. Apparently, hyperalgesia and tolerance after short-term exposure of remifentanil for anaesthesia might even co-exist. Some insight into this was in a study[2] of postoperative pain scores in patients after major abdominal surgery who had received high-dose remifentanil (mean dose 0.3 $\mu g\ kg^{-1}\ min^{-1}$) perioperatively. In this study, patients with high-dose remifentanil anaesthesia required morphine earlier and needed greater doses to achieve satisfactory analgesia, after operation. Another observation in this study was that this increased morphine demand extended for several hours after operation. The authors explained their findings in the context of the development of acute opioid tolerance due to greater morphine requirement for the high-dose remifentanil group. Furthermore, the observation of the increased and prolonged morphine demand after operation was associated with the development of hyperalgesia. The study supported the possibility of the co-existence of tolerance and hyperalgesia in high-dose remifentanil anaesthesia.

Clinical pain models using healthy volunteers have been utilized to investigate the effect of the short-term administration of opioids and provide direct evidence for the existence of opioid-induced hyperalgesia.[3–7] In 2007, Schmidt

and colleagues[8] reported opioid-induced hyperalgesia in patients after surgical interventions using remifentanil for anaesthesia by including additional outcome measures rather than monitoring only pain levels and morphine requirements after operation. They studied patients undergoing eye surgery with isoflurane and remifentanil anaesthesia. Patients received either a high (0.4 μg kg^{-1} min^{-1}) or a low (0.1 μg kg^{-1} min^{-1}) dose of remifentanil. Pain assessment at the surgical site and postoperative compared with preoperative baseline measurements at other sites with cold and cold pressor test were evaluated 30 and 90 min after cessation of remifentanil infusion. Once patients with pain at the surgical site were excluded, only high-dose remifentanil anaesthesia was associated with the development of hyperalgesia to painful pressure. Interestingly, none of the patients studied developed a positive response to the cold and cold pressor test. The mechanism of the differences in response to different types of stimuli is unknown, but the authors suggested an involvement of different neurones carrying signals for different types of nociception. Mechanical pressure pain is thought to be carried by Aβ-fibres, with Aδ-fibres being responsible for cold detection. It could be argued that opioid-induced hyperalgesia may have selective effects on different neurones.

Direct measurements supportive of opioid-induced hyperalgesia were also reported in patients undergoing remifentanil-based anaesthesia. A study of patients undergoing major abdominal surgery investigated the hyperalgesic effects of remifentanil and ketamine.[9] In patients who received intraoperative high-dose remifentanil (0.4 μg kg^{-1} min^{-1}), larger areas of hyperalgesia surrounding the wound were observed accompanied by the request of higher doses of postoperative opioid for pain control. Interestingly, patients who received either low-dose remifentanil (0.05 μg kg^{-1} min^{-1}) alone, or higher-dose remifentanil and ketamine, showed similar areas of hyperalgesia and required similar doses of postoperative morphine.[9] It is important to note that the study was designed to investigate perincisional allodynia and hyperalgesia induced by remifentanil rather than investigating generalized opioid-induced hyperalgesia.

An elegant study of acute tolerance in healthy subjects using remifentanil examined whether a short-term administration of a clinically relevant remifentanil dose ranging between 0.065 and 0.13 μg kg^{-1} min^{-1} was associated with the development of tolerance to analgesic, respiratory depressant, and sedative opioid effects.[10] Pain outcome measures were the response to heat pain, electrical pain, and cold pressure pain. In this study, no significant differences were detected between any pain test results obtained before and after remifentanil and the opioid doses were not associated with the development of acute tolerance. However, it remains to be seen whether tolerance may develop differently in pain conditions other than acute pain.

Another aspect which has not been investigated is the potential of a disease progression on changes of sensory thresholds. If such changes occur and sensory abnormalities are present before operation, this in turn could blur postoperative sensory outcome measures and therefore might compromise the investigation of opioid-induced hyperalgesia. The German Network on Neuropathic Pain (DNFS) established a standardized quantitative sensory testing (QST) protocol to investigate the somatosensory thresholds in healthy subjects and in patients with neuropathic pain.[11] This comprehensive QST battery uses sensory threshold reference values from healthy volunteers to identify somatosensory abnormalities in patients with chronic pain. Similarly, reference values from healthy subjects could be used to establish normal sensory functioning in patients before anaesthesia. In addition, the use of standardized tools and a standardized testing protocol would allow a direct comparison between different studies investigating opioid-induced hyperalgesia.

In a recent editorial in the *British Journal of Anaesthesia*, Colvin and Fallon[12] summarized the current understanding of the pathomechanism of opioid-induced tolerance and hyperalgesia. On the basis of predominantly animal experimental results, they indicated that both peripheral and central changes in nociceptive processing are involved in opioid-induced hyperalgesia. Such changes could be attributed at the pre- and postsynaptic levels affecting NMDA receptor activity, G-proteins, and intracellular systems. Despite the extensive basic science evidence for opioid-induced hyperalgesia, they emphasis the lack of good quality clinical research.

In reviewing current literature, clinical data indicate that early postoperative pain scores and subsequent greater demand of opioids could be attributed to tolerance, and the greater requirement for opioids at a later recovery stage could be associated with opioid-induced hyperalgesia after high-dose remifentanil anaesthesia. Whether opioids given after operation for tolerance-induced pain in patients can potentially aggravate opioid-induced hyperalgesia has been not established. Clinical pain models provide us with some important information regarding outcome measurements for direct assessment of the effect of opioids on sensory thresholds, for example, opioid-induced hyperalgesia. Currently, there are only limited data available for the direct assessment of the effect of opioids on sensory thresholds clinically after opioid anaesthesia. Future studies using opioid anaesthesia in patients should be designed to include additional outcome measures beyond measurement of pain levels and opioid consumption. These could be measurements such as mechanical detection thresholds using von Frey filaments, mechanical pain sensitivity, and wind up ratio assessed both by pinprick devices and pressure pain threshold using an algometer, encompassing the test of functionality for Aβ-fibre, Aδ-fibre, C-fibre, and deep C-fibre/Aδ-fibre, retrospectively.[11] Tests should be performed before anaesthesia in an area separate from the surgical site and for several hours after operation. Such an approach might identify opioid-induced hyperalgesia at an early stage and subsequently differentiate it from tolerance. This has clinical importance, as tolerance can be overcome by dose

escalation, while opioid-induced hyperalgesia may be aggravated by the same intervention. Further studies which help to clarify the potential role of perioperative opioids and untreated serious pain in the development of chronic pain are also urgently needed.

Conflict of interest

None declared.

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