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## Editorial Views

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### Preemptive Hyperalgesia, Not Analgesia?

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This Editorial View accompanies the following article: Celerier E, Rivat C, Jun Y, Laulin J-P, Larcher A, Reynier P, Simonnet G: Long-lasting hyperalgesia induced by fentanyl in rats: Preventive effect of ketamine. *ANESTHESIOLOGY* 2000; 92:465-72.

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DESPITE its logical appeal and strong support in animal experiments, there is relatively little evidence in humans after surgery for the phenomenon of "preemptive analgesia." Thus, providing intense analgesia from large doses of systemic or epidural-spinal medications before and during surgery (even extending into the acute postoperative period) appears to exert no or only modest effects on subsequent pain experience or analgesic requirements. The study by Celerier *et al.* [1] may give us a clue for one reason for this failure of a strong clinical effect by preemptive analgesic therapy.

Classically, we think that opioids produce analgesia and side effects after acute administration, and

tolerance and dependence after chronic administration. More recently, it has become recognized that tolerance can develop rapidly from acute opioid exposure as well, both in animals [2] and in humans. [3] Perhaps, therefore, one of the reasons for the failure to consistently observe a sustained effect of preemptive analgesia with large doses of opioids is an acute increase in dose requirement after such large doses because of acute development of tolerance.

The current study provides a different reason for the failure of preemptive analgesia from opioids. In the study by Celerier et al. [1] study, rats received systemic fentanyl over a short time (four doses in 1 h). Fentanyl produced, as expected, acute antinociception to a noxious stimulus, an effect that lasted a few hours. After this, rats developed hyperalgesia (a reduction in withdrawal threshold to a presumably normally noxious stimulus), an effect that lasted for days thereafter. The more the fentanyl administered acutely, the greater this hyperalgesic effect. If such an effect occurs in humans, then part of the lack of preemptive analgesia, at least from systemic opioids, could reflect development of sustained hyperalgesia from previous opioid exposure.

It turns out that both of these phenomena (tolerance and delayed hyperalgesia from opioid exposure) may reflect similar mechanisms. Activation of excitatory glutamate receptors of the *N*-methyl-D-aspartate (NMDA) type in the central nervous system after noxious stimulation underlies the transmission of signals interpreted as pain and also underlies the development of hyperalgesic states. The first clue that an NMDA action could be related to opioid tolerance and hyperalgesia was the report that morphine tolerance and dependence could be inhibited by treatment with an NMDA antagonist. [4] This led to a series of studies in animals that suggest cross-talk between opioid receptors and NMDA receptors on the same cell. The underlying hypothesis [5] is that opioid receptor activation results in stimulation of protein kinase C (PKC), an enzyme that phosphorylates several target proteins, including the NMDA receptor. Phosphorylation of the NMDA receptor results in a release of the  $Mg^{2+}$  block, entry of  $Ca^{2+}$  into the cell, and activation of a series of cascades that can lead to opioid receptor down-regulation (underlying tolerance) and hyper-responsiveness (underlying hyperalgesia). As anticipated by this hypothesis, previous administration of the NMDA antagonist ketamine prevented fentanyl-induced hyperalgesia in the current study.

Are these results relevant to the clinical experience with acute opioid exposure intra- and postoperatively in surgical patients? Some studies suggest they are. For example, women undergoing total abdominal hysterectomy who receive a large dose of intravenous fentanyl during induction of anesthesia (15  $\mu$ g/kg) have greater pain and opioid requirements in the first several hours after surgery than those receiving a smaller fentanyl dose (5  $\mu$ g/kg). [6] Additionally, the area of hyperalgesia to mechanical probing surrounding a surgical wound is dramatically reduced when a small intravenous dose of ketamine is added to morphine. [7] With the short-lived opioid remifentanyl one can now produce intense opioid receptor activation in nearly all patients intraoperatively, and these considerations suggest that this may not be good; in that, rapid and extensive tolerance to this agent has been shown in humans [3] and perhaps just as dramatic hyperalgesia could be produced.

Should we abandon the use of large or even moderate doses of opioids before and during surgery based on these concerns? Probably not. First, several phenomena occur in a more exaggerated manner in rats than in humans, including the very rapid development of tolerance to opioids. Second, it should be recognized that the hyperalgesia observed in the current study is quite small, and could be clinically unimportant. Third, patients receiving intraoperative fentanyl (at least in a modest dose (5  $\mu$ g/kg) have higher, not lower, pain thresholds to mechanical stimulation than do patients who have not received fentanyl. [8] Finally, other studies have failed to observe increased postoperative pain and opioid consumption with high-dose intraoperative opioid treatment. [9]

Should we begin routine treatment with ketamine to enhance opioid analgesia intra- and postoperatively

and to prevent tolerance and hyperalgesia development? Probably not. Although ketamine does reduce wound hyperalgesia after surgery, this does not equate to lowered pain reported by the patient, or even lowered morphine requirements. [2] Ketamine can produce unwanted hemodynamic and psychologic effects, and its routine use in this setting is not justified at this time. Other agents with fewer side effects that also reduce NMDA receptor activation, such as methadone and dextromethorphan, are being investigated.

In summary, Celerier et al. [1] confirm, using clinically available drugs, that we may be contributing to postoperative pain, not to postoperative analgesia, by use of large doses of opioids intraoperatively. There are many good reasons to administer opioids, and, in select cases, large doses of opioids, during surgery. Studies to date should not dissuade us from such appropriate use. However, a growing body of evidence suggests that cellular events initiated by opioid receptor activation may produce acute and long-term deleterious consequences, and point the way toward combination drug therapy to maintain the desired drug effects while minimizing the deleterious ones.

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