

Ketamine Improves the Management of Exaggerated Postoperative Pain Observed in Perioperative Fentanyl-treated Rats

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Background: Although opioids are unsurpassed analgesics, experimental and clinical studies suggest that opioids activate *N*-methyl-D-aspartate pronociceptive systems leading to pain hypersensitivity and short-term tolerance. Because it is difficult in humans to differentiate pain from hyperalgesia during the postoperative period, the authors performed experimental studies with fentanyl using the rat incisional pain model for evaluating relations between hyperalgesia and short-term tolerance. Because *N*-methyl-D-aspartate receptor antagonists oppose both pain hypersensitivity and tolerance induced by opioids, the authors examined the capability of ketamine for improving exaggerated postoperative pain management.

Methods: During halothane anesthesia, a hind paw plantar incision was performed in rats receiving four fentanyl subcutaneous injections (100 µg/kg per injection, every 15 min). In some groups, three subcutaneous ketamine injections (10 mg/kg per injection, every 5 h) were performed in saline- or fentanyl-treated rats. One day after surgery, the analgesic effect of morphine (2 mg/kg subcutaneous) was tested. Analgesia, mechanical hyperalgesia, tactile allodynia, and pain score were assessed for several days using the paw pressure vocalization test, the von Frey application test, and the postural disequilibrium test.

Results: Fentanyl induced analgesia but also produced exaggerated postoperative pain as indicated by the enhancement of hyperalgesia, allodynia, and weight-bearing decrease after hind paw plantar incision. Ketamine pretreatment prevented such a fentanyl-induced enhancement of postoperative pain and improved its management by morphine.

Conclusions: By opposing postoperative pain hypersensitivity and subsequent short-term tolerance induced by perioperative opioid use, ketamine not only improves exaggerated postoperative pain management but also provides better postoperative rehabilitation.

DURING the last decade, hyperalgesia and allodynia have been reported as new adverse effects related to short-term opioid use.¹⁻⁵ In rats, it has been shown that a single fentanyl administration enhances inflammatory hyperalgesia induced by hind paw injection of the proin-

flammatory drug carrageenan.⁶ Opioid-induced hyperalgesia and allodynia have also been observed in human volunteers after analgesia produced by various opioid injections.⁷⁻¹⁰ As a result, although opioids remain the strongest analgesics for pain management, we must now consider that they may also—paradoxically—facilitate postoperative pain in humans.^{11,12}

The concept of short-term tolerance emerges simultaneously. A single injection of fentanyl or heroin in rats elicited a dose-reduction of the analgesic effect of a subsequent opioid administration.^{1,13} Similar animal studies convincingly demonstrate that constant-rate infusions of alfentanil quickly produce a profound decrease in analgesia.⁵ Short-term tolerance has also been observed in human volunteers 1–2 h after the beginning of low-dose remifentanyl infusion.¹⁴ In clinical practice, fentanyl or remifentanyl administration for abdominal^{11,12,15} or orthopaedic surgeries¹⁶ increases morphine requirement, suggesting short-term tolerance. It seems that the larger the intraoperative fentanyl or remifentanyl dose is, the greater the postoperative opioid requirement is.¹²

However, the clinical relevance of short-term tolerance and opioid-induced hyperalgesia remains unclear and controversial in the recent literature.^{17,18} As an *N*-methyl-D-aspartate (NMDA) receptor antagonist may oppose both pain hypersensitivity and tolerance induced by opioids in experimental models, it has been suggested that these two phenomena may have common mechanisms.¹⁹⁻²¹ Therefore, an original hypothesis suggests that tolerance, especially short-term tolerance, is not mainly due to a decrease in opioid effectiveness, as described classically, but might result from an enhancement in pain sensitivity leading to an apparent decrease in the effectiveness of morphine.^{3,22}

Because easy differentiation of pain due to surgical lesion from hyperalgesia related to sensitization induced by both nociceptive inputs and opioids during the postoperative period is difficult in humans, we performed a series of experimental studies with fentanyl on rats using the incisional pain model,²³ well recognized for mimicking perioperative and postoperative pain. To evaluate relations between hyperalgesia and short-term tolerance and also to better differentiate changes in pain sensitivity from pain level, we simultaneously determined (1) pain sensitivity by measuring nociceptive thresholds using standard tests as the paw pressure vocalization and von Frey tests and (2) pain score using a behavioral test

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assessing the spontaneous weight-bearing changes induced by a unilateral hind paw incision. In the first phase, we evaluated the long-lasting enhancement of hyperalgesia, allodynia, and pain score produced by perioperative fentanyl use. In the second phase, we examined the preventive effect of an NMDA receptor antagonist, such as ketamine, on the exaggerated postoperative pain observed in fentanyl-treated rats and its ability to improve the analgesic effectiveness of morphine during the postoperative period.

Materials and Methods

Animals

Experiments were performed on adult male Sprague-Dawley rats (Charles River Laboratories, l'Abresle, France) weighing 300–350 g, housed in groups of four per cage with a 12-h light–12-h dark cycle (lights on at 7:00 AM) at a constant room temperature of $23^{\circ} \pm 2^{\circ}\text{C}$. The animals had access to food and water *ad libitum*. Pharmacologic tests and care of the animals were conducted in accordance with the *Animal Care and Use Manual* of the National Institutes of Health (1999).²⁴ This study, including care of the animals involved, was conducted according to the official edict presented by the French Ministry of Agriculture (Paris, France) and the recommendations of the Helsinki Declaration. At the end of the experiment, the rats were euthanized with pentobarbital sodium (120 mg/kg). Accordingly, these experiments were conducted in an authorized laboratory and under the supervision of an authorized researcher (J.-P. L.).

Drugs

Fentanyl citrate, ketamine hydrochloride, morphine, and naloxone (Sigma-Aldrich, Saint-Quentin Fallavier, France) were dissolved in physiologic saline (0.9%). Fentanyl (100 $\mu\text{g/kg}$), ketamine (10 mg/kg), morphine (2 mg/kg), and naloxone (1 mg/kg) were administered subcutaneously (1 ml/kg body weight). Control animals received an equal volume of saline injections. Penicillin G (30,000 U), dissolved in physiologic saline, was injected in triceps muscle (nonoperated side) just before surgery. An ointment with 2% Fucidine (Léo, St. Quentin-en-Yvelines, France), and Primyxine (oxytetracycline hydrochloride and polymyxine B sulfate; Chemineau, Vouvray, France) was placed on the wound after surgery.

Behavioral Testing

Three pain tests were used to assess pain behavior.

Mechanical hyperalgesia was measured as the threshold to a noxious mechanical stimulus. Nociceptive thresholds were determined in hand-held rats by a modification of the Randall-Selitto method,²⁵ a paw-pressure vocalization test in which a constantly increasing pressure is applied to the hind paw until the rat squeaks. The

Basile Analgesimeter (Apelex, Massy, France; stylus tip diameter, 1 mm) was used. A 600-g cutoff value was set to prevent tissue damage.

Tactile allodynia was assessed by studying withdrawal response to a nonnoxious tactile stimulus using von Frey filament application. Unrestrained rats were placed beneath a clear plastic chamber on an elevated mesh floor and allowed to acclimate. Withdrawal responses to mechanical stimulation were determined using calibrated von Frey filaments applied from underneath the cage through openings in the mesh floor to an area adjacent to the wound and to the same area on the noninjured foot. Each von Frey filament was applied once, starting with 15 mN and continuing until a withdrawal response occurred or 265 mN (the cutoff value) was reached. This was repeated three times. The lowest force from the three tests producing a response was considered as the withdrawal threshold. The cutoff value, 265 mN, was recorded even if there was no withdrawal response to this force.

Pain scoring was based on weight-bearing changes using an incapitance apparatus (Bioseb, Chaville, France) detecting changes in postural equilibrium after a hind paw injury. As previously described,²⁶ the rats were trained to stand on their hind paws in a box with an inclined plane (65° from horizontal). This box was placed above the incapitance apparatus. This allowed us to independently measure the weight that the animal applied on each hind paw. The value considered for each animal was the mean of 10 consecutive measurements. To avoid changes related to the increase of the rat body weight, the results were expressed as a percentage of total body weight. In the absence of hind paw injury, rats applied equal weight (approximately 40% of total body weight) on both hind paws, indicating a postural equilibrium.

General Procedure

On arrival in the laboratory, animals were left to become accustomed to the animal care unit for 4 days. To avoid stress resulting from the experimental conditions that might affect measurement of pain parameters, the experiments were performed by the same experimenter in quiet conditions in a test room close to the animal care unit. For 2 weeks before the experiments, the animals were weighed daily, handled gently during 5 min, and placed in the test room for 2 h (from 11:00 AM to 1:00 PM), where they were left to become accustomed to the various apparatuses. All experiments began at 11:00 AM and were performed on groups of 12 animals during the light part of the cycle.

Behavioral tests were performed on the 2 days preceding the scheduled experimental day (*i.e.*, on D_{-2} and D_{-1}) and were repeated on the experimental day (D_0), just before

surgery. Experiments were only initiated when no statistical change of the basal pain parameters was observed for 3 successive days (D_{-2} , D_{-1} , and D_0 , one-way analysis of variance, $P > 0.05$). The reference value of each pain parameter was chosen as the basal value on D_0 . The experimenter was unaware of the treatment used.

Two hours after the basal pain parameter measurement on D_0 , one fentanyl (100 $\mu\text{g/kg}$) or saline injection was performed four consecutive times every 15 min, resulting in a total dose of 400 $\mu\text{g/kg}$. Surgery was performed during halothane anesthesia just after the second fentanyl (or saline) injection. The three pain parameters were assessed 2, 4, 6, 10 h after surgery and once daily during the 8 subsequent postoperative days. In some experiments, rats were treated with three 10 mg/kg ketamine injections administered 30 min before and 4.5 and 9.5 h after the first saline or fentanyl injection. When the analgesic effect of morphine was studied on the postsurgical day (D_1), pain parameters were evaluated 30, 60, and 90 min after morphine injection. On D_8 , all rats received a naloxone injection (1 mg/kg subcutaneous), and pain parameters were measured 5 min later.

Surgical Procedure

Just before the surgery, rats were anesthetized with 1–3% halothane vaporized *via* a nose cone. The plantar aspect of the operated hind paw was prepared in a sterile manner with 5% povidone-iodine solution, and the foot was placed through a hole in a sterile drape. As previously described,²³ a 1-cm-long incision, starting 0.5 cm from the heel and extending toward the toes, was made with a No. 11 blade, through the skin and fascia of the plantar aspect of the left hind paw, including the underlying muscle. The plantaris muscle was then elevated and longitudinally incised, leaving the muscle origin and insertion intact. After hemostasis with gentle pressure, the skin was apposed with two mattress sutures of 5-0 nylon on a curved needle. The wound site was covered with an antibiotic mixture of polymyxine B, oxytetracycline, and fusidate. At the end of surgery, halothane was stopped, and rats awakened and were left to recover in their home cage.

Calculation and Statistical Analysis

Algesic indexes, represented by the area above the curve for D_1 to D_7 , were calculated for each rat by the trapezoidal method⁴ and were expressed as a mean percentage (\pm SD) of the reference index (100%: algesic index associated with hyperalgesia observed in the control group). Analgesic indexes for morphine analgesia represented by the area under the curve were similarly calculated by the trapezoidal method.

To evaluate the time-course effects of treatments on

pain parameters (basal reference value: presurgical value on D_0 for all experiments and the first measure value on D_1 for morphine analgesia), an analysis of variance followed by *post hoc* analysis using the Dunnett test was performed on D_0 , and another was performed on the days after the treatments in each group. The Mann-Whitney test was used to compare the algesic indexes. The paired Student *t* test was used for comparing the hyperalgesic effect induced by naloxone on D_8 . The statistical significance criterion was $P < 0.05$.

Results

Ketamine Effects on the Incisional Pain Model

As expected, the unilateral left hind paw plantar incision produced a significant decrease of the nociceptive threshold (Dunnett test, $P < 0.05$) as measured with the paw pressure vocalization test (mechanical hyperalgesia for 2 days; fig. 1A) and the von Frey application (tactile allodynia for 5 days; fig. 1B). Moreover, incision of the plantar surface of the hind paw produced a significant reduction in weight bearing for 2 days (fig. 1C). Naloxone administration on D_8 , after rats had returned to normal pain parameter values, induced no significant decrease in the values assessed with those three tests.

When injected three times every 5 h on D_0 , ketamine had no effect on pain parameter changes induced by the hind paw incision (two-way analysis of variance, $P > 0.05$). No difference in algesic index (Mann-Whitney test, $P > 0.05$) was observed in ketamine-treated rats *versus* saline-treated control rats (figs. 1A–C, insets). Naloxone administered on D_8 did not induce any significant difference according to the three test values between both groups.

Fentanyl Enhancement of Pain Behavior Induced by Plantar Hind Paw Incision

As expected, fentanyl administration on D_0 (four boluses of 100 $\mu\text{g/kg}$) initially induced an analgesic effect as revealed in both paw pressure vocalization and von Frey tests (Dunnett test, $P < 0.05$). Interestingly, fentanyl totally prevented the weight-bearing decrease induced by the incision for 2 h and partially opposed it 4 h after its administration. This analgesic effect disappeared 6 h later. Consecutive daily measurement of pain parameters showed enhancement of mechanical hyperalgesia, tactile allodynia, and weight-bearing decrease for 5, 5, and 3 days, respectively (Dunnett test, $P < 0.05$; figs. 2A–C). The algesic index (figs. 2A–C, insets) indicated a significant increase for the three pain parameters (Mann-Whitney test, $P < 0.05$). When injected on D_8 , naloxone induced hyperalgesia, allodynia, and weight-bearing decrease in fentanyl-treated rats (Student *t* test, $P < 0.05$).

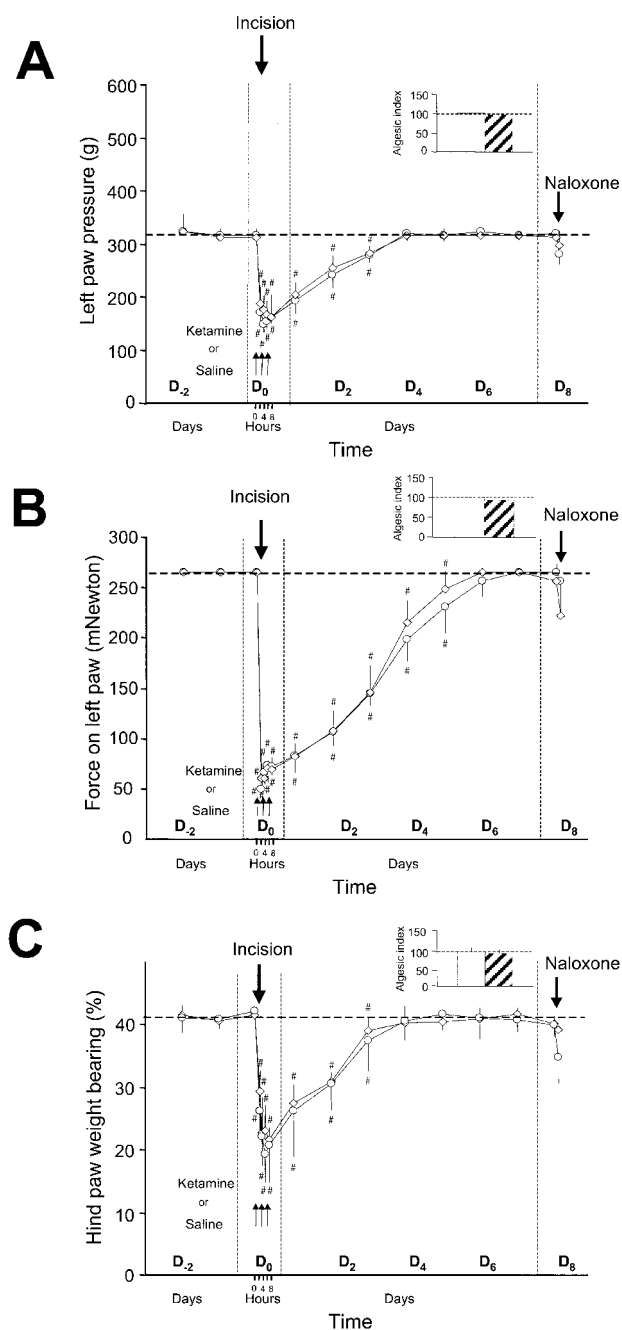


Fig. 1. Effects of ketamine on mechanical hyperalgesia (A), tactile allodynia (B), and weight-bearing changes (C) induced by left hind paw plantar incision. A hind paw plantar incision was realized on rats during halothane anesthesia on D₀. Three injections of ketamine (3×10 mg/kg, administered subcutaneously; $n = 12$) or saline ($n = 12$) were performed. The first one was performed 30 min before the surgery, and the following injections were performed every 5 h. The three pain parameters were evaluated before surgery on D₋₂, D₋₁, and D₀; 2, 4, 6, and 10 h after surgery on D₀; and subsequently once daily for 8 days. At the end of the experiment (D₈), all rats were injected with naloxone (1 mg/kg subcutaneous), and the three pain parameters were measured 5 min later. (Inset) Algesic index showing the variations of mechanical hyperalgesia, tactile allodynia, and weight bearing on the days after the incision. Pain parameter values and algesic index are expressed as mean \pm SD. # Dunnett test, $P < 0.05$ compared with the D₀ basal value. * Dunnett test, $P < 0.05$ for comparison between groups. \$ $P < 0.05$, Mann-Whitney test for algesic index comparison. Open circles = saline-treated rats; open diamond = ketamine-treated rats.

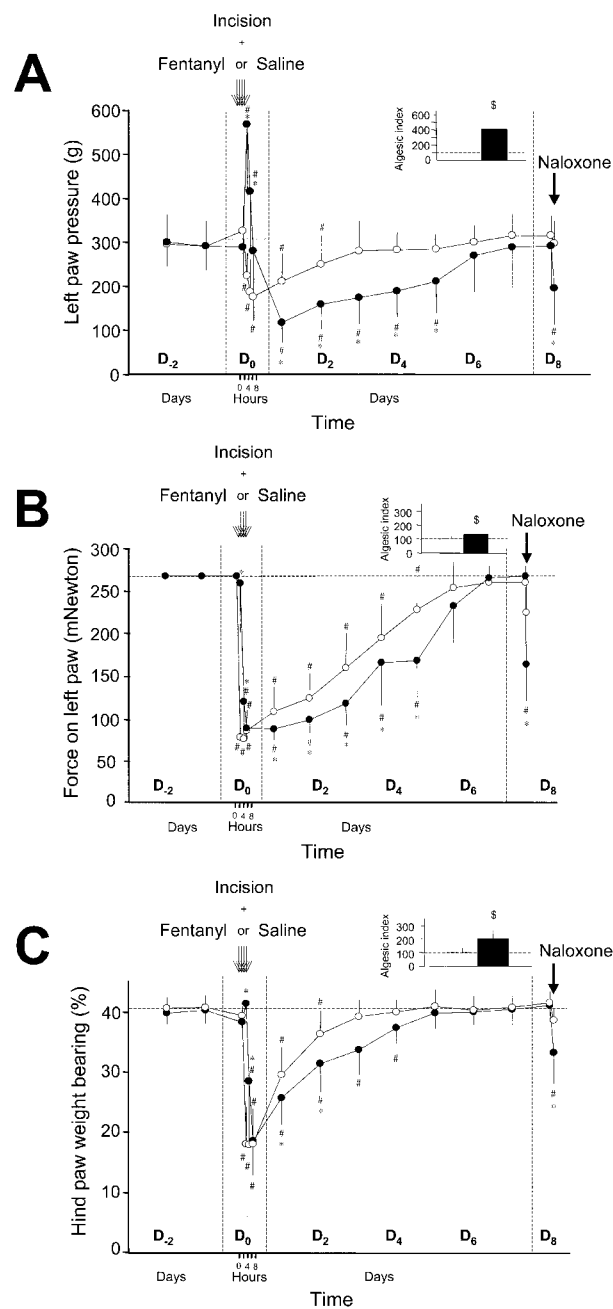


Fig. 2. Effects of fentanyl mechanical hyperalgesia (A), tactile allodynia (B), and weight-bearing changes (C) induced by left hind paw plantar incision. A hind paw plantar incision was realized on rats during halothane anesthesia on D₀. One fentanyl (100 µg/kg) or saline injection was performed four consecutive times every 15 min, resulting in a total dose of 400 µg/kg subcutaneously administered ($n = 12$). Surgery was performed just after the second fentanyl injection. The three pain parameters were evaluated before surgery on D₋₂, D₋₁, and D₀; 2, 4, and 6 h after surgery on D₀; and subsequently once daily for 8 days. At the end of the experiment (D₈), all rats were injected with naloxone (1 mg/kg subcutaneous), and the three pain parameters were measured 5 min later. (Inset) Algesic index showing the variations of mechanical hyperalgesia, tactile allodynia, and weight bearing on the days after the incision. Pain parameter values and algesic index are expressed as mean \pm SD. # Dunnett test, $P < 0.05$ compared with the D₀ basal value. * Dunnett test, $P < 0.05$ for comparison between groups. \$ $P < 0.05$, Mann-Whitney test for algesic index comparison. Open circles = saline-treated rats; filled circles = fentanyl-treated rats.

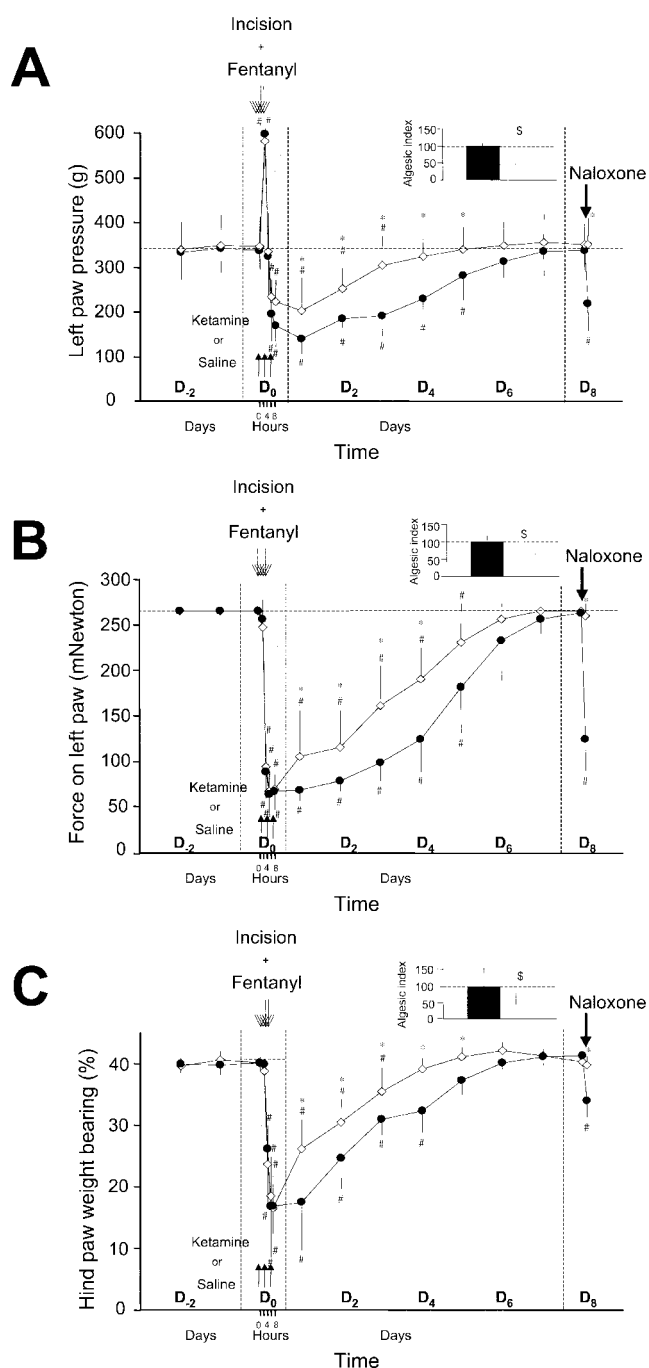
Fig. 3. Effects of ketamine on the fentanyl enhancement of mechanical hyperalgesia (A), tactile allodynia (B), and weight-bearing changes (C) induced by hind paw plantar incision. A hind paw plantar incision was realized on rats during halothane anesthesia on D₀. One fentanyl (100 µg/kg) or saline injection was performed four consecutive times every 15 min, resulting in a total dose of 400 µg/kg subcutaneously administered (n = 12). Surgery was performed just after the second fentanyl injection. Three ketamine (3 × 10 mg/kg; n = 12) or saline boluses (n = 12) were subcutaneously administered. The first one was performed 30 min before surgery, and the following injections were performed every 5 h. The three pain parameters were evaluated before surgery on D₋₂, D₋₁, and D₀; 2, 4, 6, and 10 h after the surgery on D₀; and subsequently once daily for 8 days. At the end of the experiment (D₈), all rats were injected with naloxone (1 mg/kg subcutaneous), and the three pain parameters were measured 5 min later. (Inset) Algesic index showing the variations of mechanical hyperalgesia, tactile allodynia, and weight bearing on the days after the incision. Pain parameters values and algesic index are expressed as mean ± SD. # Dunnett test, *P* < 0.05 compared with the D₀ basal value. * Dunnett test, *P* < 0.05 for comparison between groups. § Mann-Whitney test for comparison algesic indexes, *P* < 0.05. Filled circles = saline-fentanyl-treated rats; open diamond = ketamine-fentanyl-treated rats.

Preventive Effect of Ketamine on Fentanyl Enhancement of Pain Behavior Induced by Plantar Hind Paw Incision

Ketamine administration during the perioperative period on D₀ (3 boluses of 10 mg/kg) had no effect on fentanyl-induced analgesia on D₀ (fig. 3). Nevertheless, ketamine strongly reduced the enhancement of hyperalgesia, allodynia, and weight-bearing decrease induced by perioperative fentanyl administration (figs. 3A-C; Dunnett test and Student *t* test, *P* < 0.05 for pain parameters and algesic index, respectively). In ketamine-treated rats, on D₀, we observed no naloxone-precipitated hyperalgesia, allodynia, or weight bearing decrease as observed in fentanyl-treated rats on D₈ (Student *t* test, *P* < 0.05).

Improvement of Postoperative Morphine-induced Analgesia by Ketamine in Fentanyl-treated Rats

When administered 1 day after surgery in rats treated with fentanyl on D₀, morphine induced an analgesic effect as observed by the nociceptive threshold increase (Dunnett test, *P* < 0.05 by comparison with the D₁ basal value; figs. 4A and B) in saline- or ketamine-treated rats. A partial reduction of weight-bearing decrease by morphine was observed in the non-ketamine-treated group (Dunnett test, *P* < 0.05) when compared with the D₀ basal value. Although no difference in analgesic index of morphine was observed between the two experimental groups (Mann-Whitney test, *P* > 0.05; figs. 4A-C, insets), morphine was more effective in ketamine-treated rats because it totally suppressed the weight-bearing decrease (Dunnett test, *P* > 0.05 when compared with the D₀ basal value). As seen in the previous experiment (fig. 3), naloxone-precipitated hyperalgesia, allodynia,



and weight-bearing decrease were not observed in ketamine-treated rats, unlike in fentanyl-treated rats on D₈ (Student *t* test, *P* > 0.05).

Discussion

There are two main findings in this study. The first one is that fentanyl induced analgesia as described classically but also enhanced postoperative pain in a surgical pain model²³ via an enhancement in pain sensitivity. The second finding is that perioperative use of an NMDA

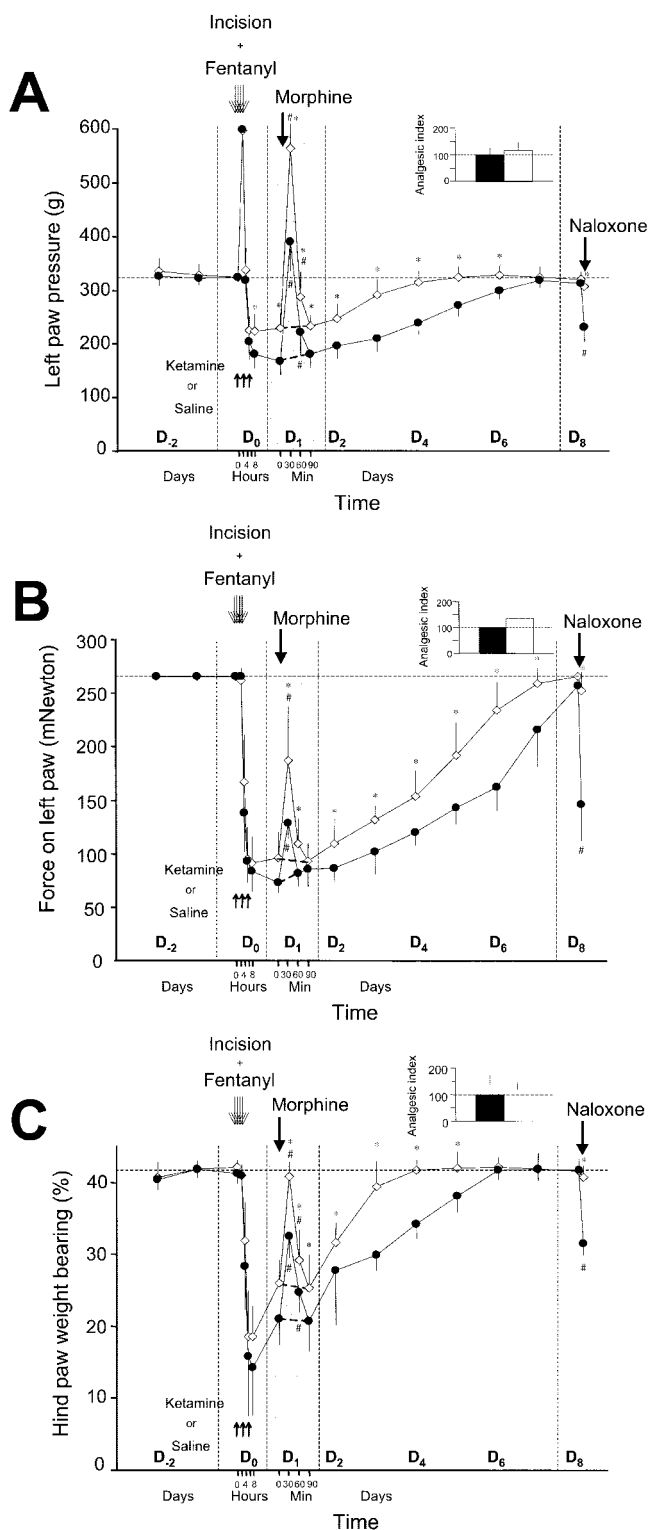


Fig. 4. Effect of ketamine on the analgesic effect of a single morphine injection (2 mg/kg subcutaneously on D₁) on mechanical hyperalgesia (A), tactile allodynia (B), and weight-bearing changes (C) induced by hind paw plantar incision in fentanyl-treated rats. A hind paw plantar incision was realized on rats during halothane anesthesia on D₀. One fentanyl (100 µg/kg) or saline injection was performed four consecutive times every 15 min, resulting in a total dose of 400 µg/kg subcutaneously administered (n = 12). Surgery was performed just after the second fentanyl injection. Three ketamine (3 × 10 mg/kg; n = 12) or saline boluses (n = 12) were subcutaneously administered. The first one was performed 30 min before the surgery, and the following injections were performed every 5 h. The three pain parameters were evaluated before surgery on D₋₂, D₋₁, and D₀; 2, 4, 6, and 10 h after the surgery on D₀. On D₁, morphine (2 mg/kg) was subcutaneously injected, and the three pain parameters were evaluated 30, 60, and 90 min later. Next, the three pain parameters were subsequently evaluated once daily for 8 days. At the end of the experiment (D₈), all rats were injected with naloxone (1 mg/kg subcutaneous), and the three pain parameters were measured 5 min later. (Inset) Analgesic index showing the reduction of mechanical hyperalgesia, tactile allodynia, and weight bearing after morphine injection (D₁). Pain parameters values and analgesic index are expressed as mean ± SD. # Dunnett test, *P* < 0.05 compared with the D₁ basal value. * Dunnett test, *P* < 0.05 for comparison between groups. Filled circles = saline-fentanyl-treated rats; open diamond = ketamine-fentanyl-treated rats.

therefore improving its management? It has been widely reported that major surgeries with opioid-based anesthesia are associated with frequent incidence of severe postoperative pain.^{11,12,16,27} Pathophysiologic mechanisms underlying such hyperalgesia are still poorly understood. From a medical viewpoint, a postoperative pain excess is usually explained by excessive nociceptive inputs after surgery and its subsequent lesions. An alternative explanation is that exaggerated postoperative pain is not mainly associated with an excess of nociceptive inputs alone but also results from the development of hypersensitivity to nociceptive stimuli enhanced by perioperative opioid use.²⁰ Therefore, a critical question for improving postoperative pain management is to know whether short-term tolerance, classically defined as a reduction of analgesic effects after a single use of opioids, really exists in postoperative period or whether it is only a phenomenon resulting from the development of a pain hypersensitivity to nociceptive stimuli. Although implications of opioid-induced hyperalgesia on postoperative pain have not been ignored,^{12,28} possible relations between postoperative pain enhancement and short-term tolerance have yet to be empirically evaluated in humans.

From a methodologic viewpoint, it is difficult in clinical trials to differentiate short-term tolerance from an exaggerated postoperative pain, both of them requiring exaggerated morphine consumption for their relief. Conversely, in the absence of verbal reports in animals, classic measurements of nociceptive thresholds as used in most of the experimental studies allowed assessment of only a pain sensitivity level, not a spontaneous pain

receptor antagonist such as ketamine, by preventing the development of pain hypersensitivity, reduced exaggerated postoperative pain and improved its management with morphine.

Could our results be relevant for better understanding the mechanisms of postoperative pain in humans and

level, in the absence of experimental nociceptive stimuli. Therefore, an enhancement in experimental pain sensitivity does not necessarily mean that there is spontaneous pain.²⁹ In fact, a decrease in nociceptive threshold values in animals means only that there is an exaggerated vulnerability to nociceptive inputs. To address this difficulty, we used in rats a test enabling us to quantify spontaneous postural changes reflecting spontaneous pain by independently measuring the weight that the animal applies on each hind paw after a unilateral hind paw tissue injury.^{26,30} The weight-bearing decrease aggravation observed for several days in fentanyl-treated rats was probably indicative of an exaggerated postoperative pain level when compared with non-fentanyl-treated rats. Therefore, by simultaneously assessing pain sensitivity using classic nociceptive threshold tests and an antalgic behavior test, our study suggests, for the first time, that exaggerated postoperative pain was not only associated with a surgical nociceptive input excess but most certainly was also due to pain hypersensitivity induced by perioperative opioid use itself. This indicates that perioperative opioid use may contribute to postoperative pain but not to postoperative analgesia³¹ and may be a relevant problem in humans. According to these results, we propose that exaggerated postoperative pain might consist of two components: The first one is directly related to the intensity of nociceptive inputs resulting from surgical and subsequent injuries. The second one is specifically underlain by central sensitization mechanisms that enhance the postoperative pain sensation for a given surgical nociceptive input level.^{20,32}

These results suggest that the management of postoperative pain could not be limited to antinociceptive agents such as opioids but also requires some antihyperalgesic agents able to prevent the development of pain sensitization processes and its outcomes. Because it is well recognized that nociceptive inputs *per se* may induce pain sensitization *via* NMDA-dependent systems³³ and that opioids facilitate such a phenomenon,^{6,19,20,34} this leads us to predict that a balanced analgesia associating an NMDA receptor antagonist with fentanyl might improve not only postoperative pain but also the effectiveness of morphine. We previously reported that NMDA receptor antagonists, when coadministered with heroin, prevent both hyperalgesia and tolerance induced by this potent opioid in rats without pain.²² Although the noncompetitive NMDA receptor antagonist ketamine acts on a variety of receptors,³⁵ we selected it because it has the advantage of being the most available NMDA receptor antagonist for anesthesiologists. Doses used throughout this study showed that ketamine had no analgesic effect *per se*, and it did not enhance the fentanyl analgesic effect. This is consistent with our previous data in rats with carrageenan-induced inflammatory pain.⁶ However, when given in three boluses during preoperative, perioperative, and postoperative periods

in fentanyl-treated rats, ketamine greatly reduced the enhancement of long-lasting hyperalgesia, allodynia, and weight-bearing decrease induced by perioperative fentanyl use. As a whole, this suggests that the beneficial effect of ketamine specifically results from its preventive effect on central pain sensitization triggered by nociceptive inputs and amplified by the perioperative fentanyl doses used.

According to our original hypothesis on tolerance, the preventive effect of ketamine on pain sensitization also suggests that ketamine may improve the effectiveness of postoperative morphine. Results obtained in the current study on the incisional pain model showed that morphine is more effective to reestablish postural equilibrium in ketamine-treated rats as compared with untreated rats. In fact, the comparison of both time course and area under the curve related to the analgesic effect of morphine (analgesic index) indicated that the analgesic potency of morphine was unchanged but that only prevention of exaggerated postoperative pain by perioperative ketamine use may explain the more pronounced analgesic effect of morphine.

As a whole, these data suggest that short-term tolerance observed during the postoperative phase is not mainly due to an actual decrease in the analgesic opioid potency *per se* as described classically but is related to sustained pain hypersensitivity. This confirms that hyperalgesia and short-term tolerance induced by perioperative fentanyl use are closely related phenomena and may be prevented by the NMDA receptor antagonist ketamine. Our results explain why most clinical studies reported that postoperative morphine consumption was decreased in patients who had received ketamine in association with fentanyl or remifentanyl for surgery.^{36,37}

When fentanyl was used for surgery, our results showed that ketamine-treated rats returned more rapidly to basal nociceptive threshold and normal weight-bearing values than non-ketamine-treated rats. Moreover, when injected after return to basal pain parameters on D₈, naloxone precipitated hyperalgesia in non-ketamine-treated rats, a phenomenon that was not observed in ketamine-treated rats. Apart from the hypothesis that an opioid antagonist might have negative intrinsic activity^{38,39} on μ -opioid receptors in a constitutively active state or sensitized by the opioid agonist stimulation, the fact that an opioid antagonist induced opposite response to analgesia in rats with no apparent pain or pain hypersensitivity suggests that rats with previous incisional pain and opioid histories did not return to their initial pain state but were in a new biologic state associated with a high-level balance between opioid-dependent analgesic systems and NMDA-dependent pronociceptive systems that masked one another. This is in agreement with the compensatory response hypothesis²⁰ supported by the opponent process theory.^{22,40}

From a clinical viewpoint, this suggests that a single

opioid treatment for surgery may induce pain vulnerability for a long time, a phenomenon that may be prevented by the NMDA receptor antagonist ketamine. We recently reported that rats receiving fentanyl in association with a first injection of the proinflammatory drug carrageenan showed an exaggerated hyperalgesia when a second carrageenan injection was performed 7 days later when animals had returned to basal nociceptive threshold values.⁶ As a speculation, it might mean that opioid use initiated a latent pain sensitization that would facilitate the development of chronic pain. Should this dissuade us from wide use of opioids for surgery? The response is certainly no, for at least two reasons. First, opioids are the most potent analgesics for the treatment of severe pain such as surgical pain, and second, drugs acting specifically on central sensitization are now available. As previously suggested,⁴¹ the notion that pain is closely related to the nociceptive stimulus intensity and that pain treatment may be limited to antinociceptive agents is obsolete and should be abandoned. An antihypersensitivity therapeutic strategy does not imply that effective agents must be potent analgesic agents *per se*; they must only oppose pain sensitization induced by both nociceptive inputs and opioids. By reducing pathophysiologic pain hypersensitivity without eliminating physiologic pain, new therapies using antihyperalgesic approaches might be fruitful pharmacologic strategies, thereby improving postoperative pain management and reducing detrimental side effects to achieve better postoperative rehabilitation.

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