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Influence of Timing of Administration on the Analgesic Effect of Bupivacaine Infiltration in Carrageenin-injected Rats

D. Fletcher, M.D., V. Kayser, D.Sc.,† G. Guilbaud, M.D., D.Sc.†*

Background: **Recent evidence has suggested that the timing of administration of analgesic drugs could influence their efficacy by reducing the sensitization of the nervous system induced by the nociceptive inputs, but this concept of preemptive analgesia is still debated in both clinical and basic research.**

Methods: **The model of acute inflammatory pain induced by carrageenin was used to study the influence of timing of administration of bupivacaine (0.2 ml of a 0.5% solution with 0.005 mg/ml epinephrine) on the development of hyperalgesia, edema, and increase in temperature. The animals received bupivacaine 5 min before (BUPI PRE group, n = 20) or 60 min after (BUPI POST group, n = 20) carrageenin (1 ml/kg of 1% solution) was injected into the left hind paw. Two control groups (n = 15 in each) received saline 5 min before or 60 min after administration of carrageenin. Hyperalgesia of the injected paw was evaluated by the vocalization threshold to paw pressure, edema by measuring paw circumference with a thread, and plantar temperature with a thermocouple thermometer. All measurements were done before carrageenin injection then every 30 min thereafter for 240 min. Another series (n = 24), with the same four groups was also evaluated at 24 h.**

Results: **Local injection of bupivacaine 60 min after carrageenin partially reduced the edema and hyperalgesia. The injection of bupivacaine 5 min before carrageenin was more efficient than the delayed injection and reduced hyperalgesia, edema and the increase in temperature temporarily, but did not totally prevent their development. All groups were similar at 240 min and 24 h.**

Conclusions: **These results show that a slight advantage of infiltration with bupivacaine before injury exists in this carrageenin model of acute inflammatory pain. However, this benefit is limited in time and bupivacaine did not have any preemptive analgesic effect. (Key Words: Analgesia: preemptive. Anesthetics, local: bupivacaine. Pain, acute: postoperative. Pharmaceuticals: carrageenin.)**

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BETTER understanding of the mechanisms of pain may help to improve postoperative analgesia, which is still inadequate.[1] Recent evidence from basic and clinical research has suggested that the timing of administration of analgesic drugs could influence their efficacy by reducing the sensitization of the nervous system induced by the nociceptive inputs (see reference 2). It has been suggested that the intensity of pain may be reduced in humans by the preadministration of drugs like local anesthetics or opioids leading to the concept of preemptive analgesia.[3] However, this concept is still debated and few clinical studies have confirmed the clinical significance of preemptive analgesia.[4] Among the different techniques of preemptive analgesia available, the direct infiltration of the surgical site with local anesthetic is a simple one.

Previous reports in animals using a brief nociceptive stimulus (60 min) like formalin injection, have reported contradictory results about the preemptive analgesic effect of local anesthetic drugs administered directly at the site of the tissue injury.[5,6] The intraplantar injection of carrageenin is widely used to produce a model of localized inflammatory pain.[7,8] Several behavioral and electrophysiologic studies have shown that, after injection of carrageenin, edema rapidly develops, followed by a period of hyperalgesia, which peaks between 1 and 4 h after inoculation and lasts

* Départment d'Anesthésie Réanimation, Hôpital Bicêtre, Bicêtre, France.

† Unité de Physiopharmacologie du Système Nerveux, INSERM, Paris, France.

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Address reprint requests to Dr. Fletcher: Unité de Physiopharmacologie du Système Nerveux, INSERM unité 161, 2 rue d'Alésia 75014, Paris, France.

24–96 h.[9–11] This evolution is similar to the time course of postoperative pain. Therefore, this model was used to evaluate the influence of timing of administration on the analgesic effect of bupivacaine administered at the site of tissue injury.

Methods and Materials

Animals

This study was conducted in concordance with the guidelines of the Ethical Standards of the International Association for the Study of Pain.[12] This study used 134 male Sprague-Dawley rats (weighing 200–225 g). The rats were housed in groups of 3–5 per cage, allowed free access to food and water with a natural day/night cycle, and acclimatized to the laboratory at least 8 days before the experiment.

Nociceptive Behavioral Test

Experiments were carried out in a quiet room. The vocalization thresholds to paw pressure were measured by the same experimenter (unaware of the drug injected) with the Basile analgesimeter (Apelex, Massy, France; tip diameter of the probe: 1 mm). For each rat, the control thresholds for vocalization (mean of two values) expressed in grams were determined by applying increasing pressure to the left hind paw until an audible squeak was elicited.[13] This criterion of the vocalization threshold to paw pressure was chosen according to the previous experience of our group with this test, because it represents a more integrated nociceptive behavior than the paw withdrawal.[12,13] The cutoff value was 600 g and was considered sufficient to represent an anesthetic state. The choice of a cutoff value was necessary to limit the injury of the paw and excessive stimulation of the nociceptors. For technical reasons, we limited the study to one hind paw.

Evaluation of Edema and Paw Temperature

To evaluate the edema, the plantar circumference of the injected paw was measured by a thread, to the nearest millimeter, at the metatarsal level. This technique, which is commonly used in our group, was previously evaluated and shown to be as sensitive as the measure of the volume by paw immersion.[14]

The paw temperature was evaluated with a thermocouple thermometer (Cole Parmer) as in a previous study of our group.[15] The thermometer was applied for 15 s on the plantar surface of the paw. A stable value of the paw temperature was obtained in all cases within 10–15 s.

Preparation and Administration of the Drugs

Bupivacaine with epinephrine was used as the local anesthetic drug (Marcaïne, 0.5% solution with epinephrine 0.005 mg/ml; Astra, Nanterre, France). Carrageenin (1% solution of lambda carrageenin in saline), was prepared 24 h before each experiment. The animals were not anesthetized but maintained in a plastic cylinder (20 × 30 cm) with the tail and the left hind paw pulled through a hole at the base of the cylinder. Injection was done with a 25-G needle subcutaneously.

Preliminary Studies.

Determination of the Appropriate Local Anesthetic Solution in Normal Rats. In the first experiment (n = 18) we evaluated the duration of the antinociceptive effect of various solutions of bupivacaine injected locally in the hind paw. The animals were evaluated before and after injection of the local anesthetic solution. The vocalization threshold to paw pressure was determined every 5 min until the recovery of control values in three groups:

- One group (n = 5) received either 0.15 ml saline or 0.15 ml 0.5% bupivacaine (Astra Laboratory, Marcaïne).
- A second group (n = 4) received either 0.15 ml saline or 0.15 ml 0.5% bupivacaine with epinephrine (0.005 mg/ml).
- A third group (n = 9) received either 0.2 ml saline or 0.2 ml 0.5% bupivacaine with epinephrine (0.005 mg/ml).

The cutoff value (600 g) was considered to reflect an anesthetic state of the paw and was thus used to determine the duration of the antinociceptive effect of bupivacaine. This value was reached with the first solution (0.15 ml 0.5% bupivacaine without epinephrine) during 6.6 ± 1.7 min. The addition of 0.005 mg/ml epinephrine prolonged the effect to 17.5 ± 7.5 min. The volume of 0.2 ml 0.5% bupivacaine with epinephrine induced an increase in the threshold to the cutoff value within 5 min in all animals and for a duration of 30.6 ± 0.6 min.

In all the following experiments, animals were treated with bupivacaine, 0.2 ml 0.5% solution with 0.005 mg/ml epinephrine, injected into the left hind paw. This drug was used to induce the longest possible anesthesia of the paw.

Determination of Appropriate Followup Duration in Carrageenin-injected Rats. Carrageenin 1% solution in saline was injected at a dose of 1 ml/kg. To determine the appropriate followup duration of the experiment, a group of rats (n = 7) received either 0.2 ml saline or bupivacaine 5 min before or 60 min after the injection of carrageenin. The threshold to paw pressure and the plantar circumference were measured every 30 min for 240 min then 24 h after the carrageenin injection. The data obtained at 240 min and 24 h were similar, thus the duration of the followup was limited to 240 min.

Influence of Epinephrine on the Carrageenin Inflammation. We used bupivacaine with epinephrine to obtain the longest possible anesthesia of the paw. To discard the possible bias of epinephrine action, the inflammation induced by carrageenin was evaluated in five animals receiving epinephrine (0.001 mg in 0.2 ml saline, the same concentration as for the bupivacaine solution [0.005 mg/ml]) either 5 min before or 60 min after the carrageenin injection. The vocalization threshold to paw pressure and paw circumference were evaluated every 30 min for 240 min.

Influence of the Timing of Bupivacaine Injection on the Carrageenin Inflammation for 24 h.

Experiment 1: Evaluation of the Vocalization Threshold to Paw Pressure and Edema. McQuay has suggested an appropriate method for studies that attempt to describe preemptive analgesia.[16] According to these recommendations, animals were randomly allocated to four groups:

- In two groups (n = 15 for each), 0.2 ml saline was injected either 5 min before (S PRE group) or 60 min after (S POST group) the carrageenin injection.
- In a third group (n = 20), bupivacaine was injected 5 min before the carrageenin injection (BUPI PRE group).
- In a fourth group (n = 20), bupivacaine was injected 60 min after the carrageenin injection (BUPI POST group).

The vocalization threshold to paw pressure and paw circumference were evaluated every 30 min for 240 min.

To confirm that no preemptive analgesic effect appears beyond 240 min, we conducted an additional experiment (n = 24) using the four previously described groups. In this additional experiment, the vocalization threshold to paw pressure and paw circumference were evaluated at 24 h.

Experiment 2: Paw Temperature Measurements. To avoid excessive handling of the animals, paw temperature was measured during another experiment. The temperature of the plantar paw was evaluated in three groups of additional rats (n = 5 for each) every 30 min for 240 min after the carrageenin injection:

- In one group, 0.2 ml saline was injected 5 min before the carrageenin (CONT group).
- In two groups, bupivacaine was injected 5 min before or 60 min after the carrageenin (BUPI PRE and BUPI POST groups, respectively).

Statistical Analysis

Raw data were expressed in grams for the vocalization threshold to paw pressure, in millimeters for the paw circumference or in degrees Celsius for the paw temperature. Comparisons between the groups were performed with analysis of variance (ANOVA) for repeated measures or factorial with *post hoc* analysis using the Fisher's protected least-squares difference test (PLSD test). The area under the curve was used in some cases to compare the different groups. For comparison at a particular time, the Student's *t* test with the Bonferonni correction (α divided by the number of comparisons) was used. The chi-square test was used for frequency distribution. Significance was measured at a level of $P < 0.05$.

Results

For all of the experiments, the time of carrageenin injection was considered as time zero, and results were expressed accordingly.

Experiment 1: Evolution of the Vocalization Threshold to Paw Pressure and Paw Circumference in Rats Receiving Either Saline or Bupivacaine

Control Groups. The development of acute inflammation was similar for both of the two control groups, receiving saline either 5 min before or 60 min after carrageenin injection. Two parameters were considered, the vocalization threshold and paw circumference. Overall, for both presaline and postsaline groups, at 180 min after carrageenin injection, the vocalization threshold decreased to 55% of the control value. In absolute terms, for the S PRE group the vocalization threshold decreased from 270 ± 18 g to 141 ± 18 g, and for the S POST group, the vocalization threshold

decreased from 276 ± 18 g to 141 ± 18 g (fig. 1). At 24 h, the vocalization threshold was still reduced, at 80% of the control value (additional experiment).

For both the S PRE and S POST groups, at 240 min after carrageenin administration, the injected paw circumference increased to 45% of the preinjection value. In absolute terms, for the S PRE group, the paw circumference increased from 28 ± 0.1 mm to a maximum of 40.7 ± 0.7 mm, and for the S POST group, the paw circumference increased from 28 ± 0.2 mm to a maximum of 40.7 ± 0.2 mm (fig. 2). At 24 h, a persistent 18% increase of the paw circumference was observed as compared with the preinjection value (additional experiment).

Bupivacaine-injected Groups: Evolution of the Vocalization Threshold to Paw Pressure.

BUPI PRE Group. With preadministration of bupivacaine, the vocalization threshold reached the cutoff value throughout the study in 95% of the animals. The vocalization threshold stayed at high values for a 90-min period after carrageenin injection (fig. 1). For later time points, 90–180 min, the vocalization threshold

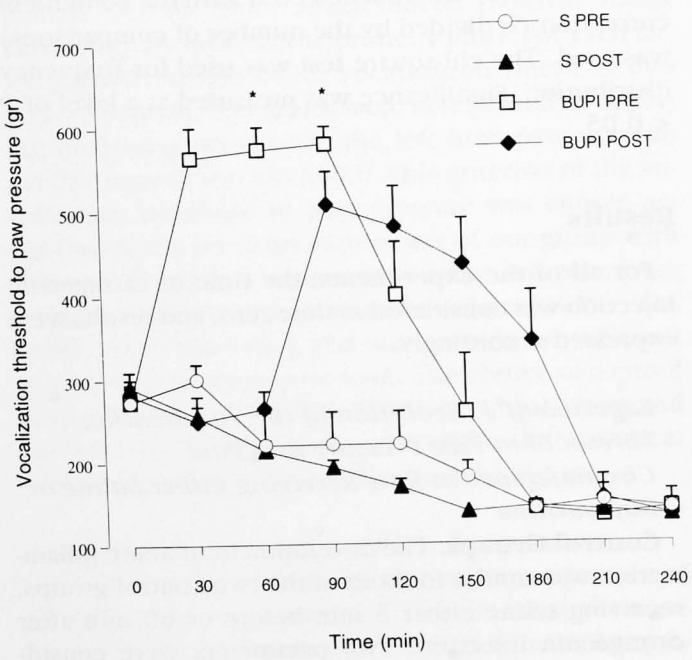

Fig. 1. Time course of the antinociceptive effect of bupivacaine on the vocalization threshold to paw pressure after injection of carrageenin. S PRE = group receiving normal saline 5 min before the injection of carrageenin; S POST = group receiving normal saline 60 min after the injection of carrageenin; BUPI PRE = group receiving bupivacaine 5 min before the injection of carrageenin; BUPI POST = group receiving bupivacaine after the injection of carrageenin. *$P < 0.05$ BUPI PRE *versus* BUPI POST. Values are expressed as mean ± SEM.

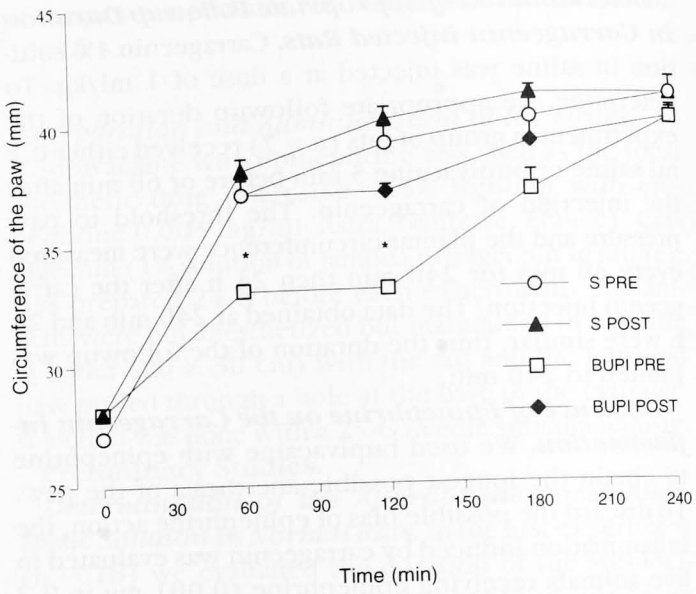

Fig. 2. Time course of the effect of bupivacaine on the edema of the paw after injection of carrageenin. S PRE = group receiving normal saline 5 min before the injection of carrageenin; S POST = group receiving normal saline 60 min after the injection of carrageenin; BUPI PRE = group receiving bupivacaine 5 min before the injection of carrageenin; BUPI POST = group receiving bupivacaine after the injection of carrageenin. *$P < 0.05$ BUPI PRE *versus* BUPI POST. Values are expressed as mean ± SEM.

decreased to 55% of the control value, reflecting the development of hyperalgesia. Overall, the vocalization threshold decreased from 273 ± 20 g, at time zero, to 141 ± 8.7 g at 180 min after carrageenin. At 24 h, the vocalization threshold was still reduced at 79% of the control value (additional experiment).

BUPI POST Group. Hyperalgesia was partially established before bupivacaine injection (reduction of 20–30% of the threshold, compared to the control value at 60 min.

With postadministration of bupivacaine, the vocalization threshold reached the cutoff value throughout the study in 60% of the animals. The elevation of the vocalization threshold lasted for 120 min after bupivacaine injection, however there was a return to hyperalgesia at 210 min after carrageenin injection (fig. 1). At 210 min, after carrageenin administration, the vocalization threshold decreased from 280 ± 17 g to 147 ± 11 g (fig. 1). At 24 h, the vocalization threshold was still reduced, at 78% of the control value (additional experiment).

Comparison between the BUPI PRE and the BUPI POST Groups. There was a significant difference be-

tween the percentage of rats reaching the cutoff value throughout the study in the BUPI PRE group and the BUPI POST group (chi-square test $P < 0.01$). In all cases, there was always a greater threshold elevation for the BUPI PRE group, up to 90 min after the carrageenin injection, as compared to the threshold elevation of the BUPI POST group ($P < 0.001$). At 120 min, the thresholds for the two groups were similar, and were not significantly different for later time points. The area under the curve illustrates that the analgesic effects observed for the BUPI PRE group are greater than the effects observed for the BUPI POST group (ANOVA, Fisher's PLSD test; $P < 0.05$).

Evolution of Paw Circumference in the Bupivacaine-injected Groups.

BUPI PRE Group. With preadministered bupivacaine, the paw circumference was significantly increased by 18%, at 60 min after carrageenin (ANOVA, Fisher's PLSD test; $P < 0.0001$). The increased paw circumference then remained stable from 60 to 120 min. The control paw circumference was 28 ± 0.1 mm, at 60 min was increased to 33 ± 0.3 mm, and at 120 min was increased to 32.6 ± 0.2 mm. After 120 min, there was a further significant increase in the paw circumference, 39.5 ± 0.5 mm at 240 min (ANOVA, Fisher's PLSD test; $P < 0.0001$), similar to the values for the control groups (fig. 2). At 24 h, a persistent 17% increase of the paw circumference was observed as compared with the preinjection value (additional experiment).

BUPI POST Group. Before carrageenin administration, the control paw circumference was 28 ± 0.1 mm. At the time of the postadministration of bupivacaine, the paw circumference was already partially increased (38% increase of the circumference as compared to the control value at 60 min: 37.2 ± 0.7 mm; ANOVA, Fisher's PLSD test; $P < 0.0001$). Between 60 and 120 min, the edema was then stabilized, with a paw circumference, at 120 min, maintained at 37 ± 0.3 mm. At later time points, the paw circumference significantly increased to a maximum value (39.4 ± 0.4 mm at 240 min; ANOVA, Fisher's PLSD test; $P < 0.0004$) similar to the values for the control groups (fig. 2). At 24 h, a persistent 18% increase of the paw circumference was observed as compared with the preinjection value (additional experiment).

Comparison between the BUPI PRE and the BUPI POST Groups. The area under the curve illustrating the evolution of the paw circumference was significantly smaller in the BUPI PRE group as compared to the BUPI POST group (ANOVA, Fisher's PLSD test; $P < 0.01$). However, preadministered bupivacaine did not prevent the development of edema, because at 240 min and 24 h after carrageenin administration, the paw circumference was similar for all three groups (a 40–45% and 17–18% increase respectively as compared to the control value; fig. 2).

Experiment 2: Evolution of Paw Temperature

BUPI PRE Group. With preadministered bupivacaine, the temperature remained similar to the control value during the first 60 min after carrageenin injection (control value: 27.5 ± 0.9°C, at 60 min: 28.9 ± 1°C). However, at later time points, the temperature increased to a maximum value of 34.7 ± 0.3°C at 240 min (fig. 3).

BUPI POST Group. Before the postadministration of bupivacaine, the temperature was already increased (control value: 28.2 ± 0.6°C, at 60 min: 32.9 ± 1.2°C). Postadministered bupivacaine reduced the elevated temperature for the 90–120-min period, after carrageenin. However, the temperature was subsequently increased reaching a maximum value of 34.6 ± 0.2°C at 240 min (fig. 3).

Comparison between the BUPI PRE and the BUPI POST Groups. In both groups, the injection of bupivacaine temporarily limited the elevation of the paw temperature. Overall, there was only a significant dif-

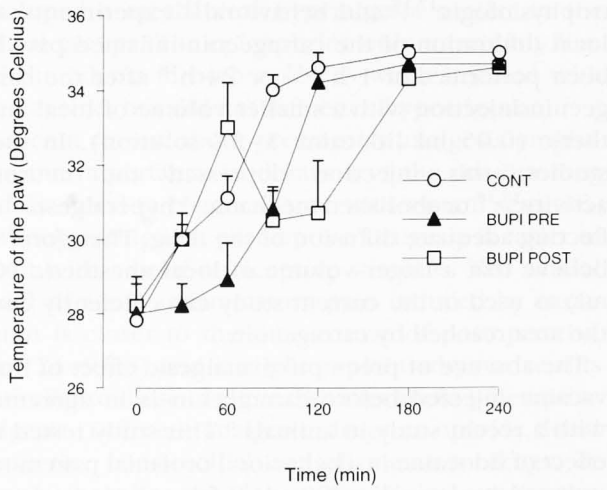

Fig. 3. Time course of the effect of bupivacaine on the temperature of the paw after injection of carrageenin. CONT = group receiving normal saline 5 min before the injection of carrageenin; BUPI PRE = group receiving bupivacaine 5 min before the injection of carrageenin; BUPI POST = group receiving bupivacaine 60 min after the injection of carrageenin. Values are expressed as mean ± SEM.

ference when considering paw temperature, between the BUPI PRE and the CONT groups (ANOVA, Fisher's PLSD test; $P = 0.0185$; fig. 3).

Discussion

Using a model of acute inflammatory pain in rat, induced by carrageenin, we did not demonstrate a significant preemptive analgesic effect of bupivacaine administered subcutaneously 5 min before the carrageenin injection. Conversely, as expected, the delayed administration of bupivacaine was effective on hyperalgesia.

In the current study, the negative results may be owing to the technique of the anesthetic block. A nerve block might be an alternative to an infiltration but would necessitate accurate localization of both the sciatic and saphenous nerves and use nontoxic doses of local anesthetic drug. The available sheathed needles that should be used are quite large (22-G for Stimulplex Braun Laboratory, Paris, France) especially when compared to the saphenous nerve in the rat, which is superficial and adjacent to a vein and an artery.

Furthermore, the behavioral test used in this study (the vocalization threshold to paw pressure) may be difficult to evaluate in case of total paralysis of the limb. To obtain preemptive analgesia, the nerve endings reached by carrageenin must be covered by the bupivacaine infiltration. In fact, in previous electrophysiologic[17,18] and behavioral[11] experiments, the local infiltration of the carrageenin-inflamed paw has been performed at 1 h[11,17] or 24 h[18] after the carrageenin injection with a smaller volume of local anesthetic (0.05 ml lidocaine 1–2% solution). In these studies, this injection depressed the neuronal activity[17,18] or abolished mechanical hyperalgesia[11] reflecting adequate diffusion of the drug. Therefore, we believe that a larger volume of local anesthetic (0.2 ml) as used in the current study can efficiently cover the area reached by carrageenin.

The absence of preemptive analgesic effect of bupivacaine injected before carrageenin is in agreement with a recent study in animals.[6] This study tested the effect of lidocaine in a behavioral orofacial pain model induced by formalin (50 μl, 2.5% solution). It was shown that the injection of lidocaine (0.05 ml, 2% solution) before formalin did not influence the appearance and the development of the second phase.

However, our results seem to contradict some aspects of a previous study evaluating the preemptive analgesic effect of local anesthetic by studying the spontaneous behavior of rats after injection of formalin (50 μl, 2.5% solution) into the hind paw.[5] In this study, the subarachnoid injection was significantly more effective on the abnormal behavior when injected before rather than after the formalin injection. This also was the case with a subcutaneous injection of 0.15 ml bupivacaine 0.5% with epinephrine performed 5 min before and 25 min after the formalin injection, whereas there was no significant effect when performed 5 min and 25 min after the formalin. The conclusion was that formalin induced a sensitization of the central nervous system that was not controlled by a delayed injection of bupivacaine or lidocaine.

We suggest several reasons that might explain these contradictory data. The spontaneous behavior used in the study of Coderre *et al.*[5] is different from the vocalization threshold to paw pressure, which is a behavioral test of provoked pain. Spontaneous pain behavior score[19] requires several minutes to be calculated and therefore is not adequate to assess a time course of analgesic effect as performed in the current study. Mainly, the formalin model has a biphasic evolution over a short period (60 min), different from the carrageenin model, which induces inflammation and a mechanical hyperalgesia of the paw for 24–96 h.[11] It seems that the concept of preemptive analgesia is more applicable to the animal models using nociceptive inputs of short duration than to persistent pain as in carrageenin inflammation. The results of a recent study seem to be in agreement with this hypothesis.[20] Preemptive intrathecal lidocaine was effective on the nociceptive responses induced by a low-concentration formalin injection (50 μl, 2.5% solution) in the rat hind paw, but less effective on the responses to higher concentration of 5 and 10% formalin (50 μl).

According to the concept of preemptive analgesia, the duration of protection may be as important as the timing of administration of analgesic drug. Therefore, our block may be too short to reveal a preemptive analgesic effect. In case of infiltration, as chosen in our study, we used the longest acting drug available. Reinjection probably would be toxic (1 mg bupivacaine already injected; more than 4 mg/kg). Since these experiments, we have used bupivacaine included in lactic acid microspheres[21] and obtained, with higher doses (5 mg bupivacaine instead of 1 mg), a 40% increase of the anesthesia related to infiltration (unpublished data). This significant increase did not reveal any preemptive effect confirming the first results.

Overall, these results suggest the importance of ongoing inputs from inflamed tissue as suggested already by Hardy *et al.* in 1950.[22] If the only way to avoid inducing central sensitization is to completely block any pain originating in the site of inflammation from the initial injury until the final healing, such analgesia is a worthy goal, but may not always be practical.

The efficacy of the delayed injection of bupivacaine was expected although it seems to contradict other data on the effect of local anesthetic drug administered peripherally after nociceptive stimuli.[23–26] In these studies, the effect of lidocaine was tested on the sensitization of the flexor reflex, after an intense thermal stimulus leading to cutaneous,[23] deep tissue injury,[25] or a chemical stimulation by mustard oil[26] or intense C fibers electrical stimulation.[24] The peripheral administration of lidocaine did not suppress the facilitation of the flexor reflex induced by these different nociceptive stimulations, and it was concluded that this facilitation was independent of the peripheral nociceptive inputs.

This efficacy of bupivacaine injected 60 min after carrageenin is in agreement with results from previous studies, using the carrageenin model, where abnormal responses in the thalamus[19] or the cortex[18] and mechanical hyperalgesia[11] were controlled by a peripheral injection of local anesthetic drug (1–2% lidocaine). Similar data, with the formalin model, have shown that a delayed injection of lidocaine can control the abnormal behaviors[6] or abolish the neuronal excitation by administration either into the site of formalin injection[27] or intrathecally.‡.

These contradictory results about the effects of the delayed peripheral block might be explained by different experimental conditions: on one side, the use of the flexor reflex in decerebrated animals, and on the other, behavioral studies in awake animals or electrophysiologic studies in anesthetized animals.

Nevertheless, although these results show that the preadministration of bupivacaine had a transient effect, it was slightly more efficient than the delayed infiltration. Factors related to inflammation as the volume, the *p*H, and the washout must be discussed to explain this difference in the direct local anesthetic effect. The different volume of the paw at the time of injection, could induce a difference in dilution and distribution of the bupivacaine. However, the volume of 0.2 ml is sufficient to allow satisfactory distribution of the bupivacaine in both groups. The washout of local anesthetic also might be different in the BUPI PRE and BUPI POST groups again because of the presence of inflammation in one group. The decrease of *p*H related to inflammation may limit the diffusion of bupivacaine in the BUPI POST group explaining part of the difference in analgesic effect. Another reasonable hypothesis could be the transient abolition by the bupivacaine, in the BUPI PRE group, of the axon reflex, which is responsible for the spread of inflammation.[28] Inflammatory substances such as substance P may not be released temporarily.[29] Bupivacaine may also reduce the leukocyte function by diminishing the number of inflammatory cells and so again the amount of algogenic substances released, as shown, *in vivo,* by the lidocaine effect on surgical wound of rats.[30] Because the peripheral nociceptors were already sensitized in the BUPI POST group, the same amount of bupivacaine was less effective than that in the BUPI PRE group and this could explain the transient difference in analgesic effect owing to the timing of injection of the bupivacaine. As shown in a preliminary study, the animals receiving epinephrine before or after the carrageenin injection developed a mechanical hyperalgesia similar to the control groups. The epinephrine only transiently limited the edema in both cases, as when injected with bupivacaine, but did not influence hyperalgesia.

A recent review about preemptive analgesia emphasizes the importance of duration of the conditioning stimulus used to trigger the nervous system sensitization¶ suggesting that preemptive analgesia is easier to obtain with a brief nociceptive stimulus. The animal model of acute inflammatory pain induced by carrageenin is closer to the time course of postoperative pain (24–96 h) and it might explain why our results are similar to those of clinical studies about preemptive analgesia. Different analgesic drugs as opioids, local anesthetic, nonsteroidal antiinflammatory drugs, or ketamine have been used to test the clinical significance of preemptive analgesia. Clinical studies about preemptive analgesia with local anesthetic drugs applied directly on the site of a superficial tissue injury, have been done for tonsillectomy,[31,32] inguinal hernia repair,[33–36] or experimental paradigm as thermal

‡ Chapman V, Dickenson AH: The effect of intrathecal pre and post treatment of lignocaine or CNQX on the formalin response of rat dorsal horn neurones. Abstracts—7th World Congress on Pain. Seattle, IASP 1993, p 469.

¶ Niv D, Devor M: Does the blockade of surgical pain preempt postoperative pain and prevent its transition to chronicity? Newsletter. Seattle, IASP, November–December: 2–7, 1993.

lesion[37] and capsaicin injection.[38] In these studies, the results about the benefit of the prevention are contradictory, describing long-term effect,[31,33,38] a short analgesic benefit,[34,36] or no analgesic benefit.[32,35,37] The model of carrageenin-induced inflammatory pain seems to reproduce data similar to the more recent clinical studies with no significant advantage for the preadministration of local anesthetic. As for animal studies, the discrepancy in the clinical studies may be attributed to the different methods employed.

In conclusion, preinfiltration with bupivacaine of carrageenin-injected paw in rat can only transiently limit the various components of inflammation including hyperalgesia. The results obtained with this model confirm recent clinical studies suggesting that preemptive analgesia with infiltration of local anesthetic has a limited clinical value.

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