Epidural Morphine Strongly Depresses Nociceptive Flexion Reflexes in Patients with Postoperative Pain

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The comparative effects of low doses (0.05–0.04 mg/kg) of epidural morphine on a nociceptive flexion reflex of the lower limb and on postoperative pain in volunteer patients were studied after orthopedic surgery on one knee. According to the stimulation parameters, it was found that 40–50 min after the injection, morphine produced an increase of 87% and 85% of the reflex threshold and of the threshold of maximal reflex response, respectively, as well as a 80–90% depression of the nociceptive responses when elicited by a constant level of stimulation. Onset of pain relief occurred by the 25th min and increased to a maximum stable level 40–50 min after the injection. These data support the hypothesis that the main site of the pain-relieving effect of epidural morphine is located directly at a spinal level. (Key words: Analgesics morphine, epidural. Anesthetic techniques: epidural morphine. Pain: postoperative. Spinal cord: reflexes.)

The spinal administration of opiates for the relief of pain is a technique that is becoming popular (see references in review by Cousins and Mather†). There is now a body of evidence, resulting mainly from animal studies, that strongly suggests that morphine induces analgesia by a powerful depressive effect on nociceptive transmission, directly at the spinal level.2–10 However, because of the lack of adequate methods for studying spinal nociceptive activity, these data have not been confirmed in humans. In such an attempt, we have shown previously that therapeutic doses of intravenous morphine (0.2–0.3 mg/kg) resulted in a strong and selective depressive effect upon lower limb nociceptive flexion reflexes in young paraplegic volunteers.11 These nociceptive flexion reflexes were shown to be well correlated with pain sensation in normal subjects.12 To a certain extent, these data confirm the animal studies concerning the direct spinal effect of morphine, but they do not deal with sensation of pain, since our patients had a complete spinal cord section from traumatic origin. In the present work, performed with normal subjects with acute postoperative pain, we observed that epidural administration of very low doses of morphine (0.03–0.04 mg/kg) resulted in pain relief that paralleled powerful depression of lower-limb nociceptive flexion reflexes.

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Materials and Methods

The aim of this study, including the whole procedure and experimental details (approved by Institutional Committee), was fully explained to four patients, who gave their informed consent according to the principles of the Helsinki Convention. These subjects (one woman, three men; ages 29–50 yr) were normal from a clinical point of view, except that they required orthopedic surgery on one knee (meniscus surgery). Surgery was carried out following epidural injection of 18 ml plain lidocaine (2%). During the experimental sessions, subjects stayed in the postoperative room and were studied from 2 to 3 h postoperatively. At the start of the electrophysiologic studies, their neurologic examination was normal, indicating no residual effects from the epidural local anesthetic. Special attention was paid to testing sensory and motor modalities. In particular, light touch, joint sense, as well as cold and noxious pinch sensations, were normal, showing that all types of peripheral sensory fibers had recovered normal function. The motor system showed normal voluntary muscular contraction and normal tendon jerk reflexes as compared with preoperative neurologic testing. As the epidural local anesthetic regressed, patients complained of postoperative pain and were then given epidural morphine.

General Experimental Procedure

In order to avoid any residual effects of lidocaine that could result in false responses, subjects were studied at least 120–150 min after the injection. After a 5-min training period, the two patterns of stimulation described below were applied on the sural nerve of the normal limb. The resulting reflex responses then were studied before (control values) and after epidural morphine (0.03–0.04 mg/kg; 5 ml) at regular 10-min intervals for 60 min. Figure 1 summarizes the paradigm of this experiment. It should be noted that this morphine dosage (total dose: 2–3 mg) is quite low compared with doses usually used for postoperative pain (between 6 and 9 mg). Respiration, heart rate, blood pressure, and level of consciousness were recorded during each session.

Electrophysiologic Procedure

Lower-limb cutaneous reflexes were studied according to a method fully described previously.13 Briefly, the sural nerve of the normal lower limb was stimulated with the
use of surface electrodes (2 cm apart) placed on the
degreased skin over the nerve along its retromalleolar path.
The stimulus consisted in a train of 20 ms duration con-
taining eight rectangular pulses of 1 ms duration each
and was delivered at a rate of 0.25 Hz by a constant-
current stimulator. Furthermore, the stimulus intensity
was measured permanently by means of a probe placed
in series on the stimulation circuit and connected to an
oscilloscope. Nociceptive flexion reflexes were recorded
from a knee-flexor muscle: the biceps femoris (capitis
brevis) muscle, with the use of surface electrodes placed
on the degreased skin overlying the muscle (fig. 2 depicts
the experimental set-up). These electrical signals were
displayed in parallel to an oscilloscope, which allowed
permanent monitoring of the experiment, and to an FM
tape recorder for further analysis of data. Under these
conditions, two patterns of stimuli were employed. The
first one consisted of stimuli of various intensities between
0 and 50 mA delivered randomly. This method allowed
the study of the recruitment curve of the nociceptive reflex
as a function of stimulus intensity, before and after
epidural morphine administration. As shown in Figure 2
for one subject, this recruitment allowed the measurement
of the reflex threshold (Tr) and of the threshold of the
maximal reflex response (Tmr). The reflex threshold (Tr)
is defined as the abscissa corresponding to the intersection
of the linear part of the recruitment regression curve with
a horizontal line placed at a 10% level of the ordinate.
Similarly, the threshold of the maximal reflex response
(Tmr) is defined as the abscissa corresponding to the in-
tersection of the recruitment regression curve with the
ordinate 100% level (corresponding to the maximal reflex
response, fig. 2). These two variables are of importance,
since we have previously shown that they were closely
 correlated with the pain threshold and with the threshold
of maximum tolerable pain, respectively.12,13 Moreover,
in normal drug-free subjects, Tr and pain threshold were
found to be homogeneously close to 10 mA (8–12 mA
range), while Tmr and maximum tolerable pain threshold
were observed at 35 mA (29–45 mA range).13,14 In con-
trast with these various intensities, the second pattern of
stimulation, with the use of a constant intensity level (1.2–
1.3 Tr), allowed the study of the effect of epidural mor-
phine on the reflex responses as a function of time. This
method was valid because we have shown in previous
studies that no significant cumulative or habituative re-
sponses were observed in such experimental conditions.14
In parallel with these electrophysiologic investigations, a
study of the quality and intensity of both electrically in-
duced and postoperative pain was performed by means
of a visual analogue scale (VAS) and a clinical pain ques-
tionnaire associated with neurologic testing performed at
regular 15-min intervals. Subsequently, in the clinical
neurophysiology laboratory, electromyographic reflex
responses were analyzed: each response was full-wave rec-
tified, integrated, and numbered via a computer program.
In order to allow interindividual comparison, numeric
data were expressed in terms of percentage of control
values or in percentage of maximal reflex response, ac-
cording to the stimulus pattern employed. Finally, these
data were statistically analyzed to provide the mean values
and variance. Significance in the variations was given by
the paired t test, while regression analysis was performed
with the use of the least-square method.

Results

In the four patients of this study, low doses epidural
morphine (2–3 mg) produced a progressive but powerful
depression of the lower limb spinal nociceptive reflexes.
This effect paralleled both the relief of postoperative and
electrically induced pain. These effects were analyzed by
studying both thresholds and suprathresholds responses
and using the two patterns of stimulation.

Effects of Epidural Morphine on the
Thresholds Responses: Tr; Tmr

Control values (mean ± SD) were 16.3 ± 1.2 mA for
Tr and 52.5 ± 6.1 mA for Tmr. As shown in figure 3 for
one subject, epidural morphine produced a progressive
increase in both Tr and Tmr from 15.5 to 29 mA (Tr)
from 46.5 to 85.6 mA (Tmr) over the 60-min period of
FIG. 2. Summary of the experimental procedure for studying lower limb nociceptive reflexes. A. Experimental set up for stimulating (STIM) the sural nerve (Sn) at the ankle level, measuring the stimulus intensity (PROBE) and recording reflex activity from the biceps femoris muscle (Bi). B. Examples of full-wave rectified electromyographic responses elicited by various stimulation intensities: 6 mA; 9 mA; 11 mA; 15 mA; and 18 mA from A to F, respectively. Calibrations: 10 ms between two bars. C. Individual example of recruitment of the nociceptive reflex as a function of stimulus intensity. The regression curve (equation and significance in the left upper part) allows the calculation of the reflex threshold shown by the lower left arrow (Tr = 10 mA) and of the threshold of the maximal reflex response, upper right arrow (Tmr = 37.5 mA). Each point represents a single numeric value for a response. Broken lines indicate the 10% (lower) and the 100% (upper) levels for the nociceptive reflex values.

study. It is of interest to notice that the onset of pain relief that occurred by the 25th–30th min following morphine administration paralleled onset of the increased thresholds (42% for Tr; 40% for Tmr). Global data obtained from all subjects are shown in figure 4. This figure shows that epidural morphine induced a homogeneous and very significant ($P < 0.001$) increase in both Tr and Tmr as a function of time as revealed by the regression curves. This increase became significant by the 20th min after morphine administration (paired t test).

**Effects of Epidural Morphine on Supraliminal Responses**

As can be seen from Figure 5 for one subject, the reflex responses did not show any sign of habituation or of sensitization in the control period. We did not observe any significant relationship between the spontaneous fluctuations of the successive single responses as a function of time during this period ($r = 0.12; n s$). In contrast, as also shown in figure 5, administration of epidural morphine resulted in a progressively powerful depression of the nociceptive reflex. When considering pooled data, a very significant relationship ($P < 0.001$) was observed in the depressive action of morphine on the reflex responses as a function of time following drug injection (fig. 6). This effect became significant (paired t test) by the 20th min (43% depression) and reached a maximum (89.8% depression) by the 50th min after morphine injection. Parallel with this effect, morphine also induced segmental pain relief, which became obvious by the 25th to 30th min and increased progressively as a function of time, until almost total relief of both postoperative and electrically induced pain as revealed by the VAS and clinical...
data testing the sensory and motor functions. It is noteworthy that these depressive and pain-relieving effects of epidural morphine were not associated, as clinically monitored, with the classical subjective opiate side effects observed when morphine is given intravenously as reported in a previous study. Furthermore, at least during the period of the experimental sessions, subjects did not describe the adverse effects of spinal morphine (e.g., itching or urinary retention) that are usually observed with higher doses of epidural morphine (6–9 mg). At the end of each experimental session, neurologic testing did not reveal any motor deficiency in the tendon jerk reflexes nor in the strength of the voluntary contraction of the normal lower limb, compared with data obtained in the pre-drug-administration period. Furthermore, there was no significant change in heart rate, blood pressure, and respiration throughout the course of each 60-min session.

Discussion

This study shows that low doses of epidural morphine can induce a powerful depression in the transmission of nociceptive spinal reflexes, which parallels the relief of acute postoperative pain in volunteer patients following orthopedic surgery on the knee. We will discuss successively some aspects of the control data and then the significance of the morphine effects in terms of the possible sites of its pain-relieving action.

As observed in the control period (pre-drug-injection), all subjects exhibited higher values in Tr (16.5 mA) and in Tmr (52.2 mA) compared with that usually obtained in normal painless subjects (Tr = 10 A; Tmr = 33.5 mA). These data can be explained by the fact that in the present report our subjects complained of postoperative pain that could result as a "pain inhibits pain" phenomenon in an increase in the nociceptive reflex thresholds and associated pain sensation, affecting both liminal (Tr) and maximal (Tmr) responses. This idea is supported by some observations from a previous study that reported that heterotopic painful stimuli (thermal, mechanical, or chemical) induced a very significant increase in Tr and in Tmr parallel with an inhibition of the associated electrically induced pain. All these data are very similar to those obtained in behavioral and electrophysiologic animal studies on the phenomenon of "pain inhibits pain," and its mechanisms seem relevant to the "Diffuse Inhibitory Controls" that have been described in the rat and suggested in humans. However, further clinical and pharmacologic experiments would be necessary for one to assess this hypothesis.
FIG. 5. Individual example (same as fig. 3) showing the effects of epidural morphine (administered at arrows) on a nociceptive reflex elicited by a constant level of stimulus intensity (1.2 Tr). Each bar corresponds to a single numbered response plotted against time. Open arrow on the upper part of the figure indicates the onset of pain relief.

The effects of low-dose epidural morphine were thus studied upon the lower-limb spinal nociceptive reflexes that were modulated by the acute postoperative pain in the contralateral knee. Even under these conditions, morphine produced a powerful depression in the nociceptive reflex activity that paralleled relief of pain. These data are in agreement with others that have shown that epidural morphine produced potent pain relief in humans (see references in Cousins and Mather). They agree with those from animal experiments showing that morphine selectively depressed the nociceptive reflexes in chronic spinal cats and dogs. Furthermore, in our study, concerned with the first 60 min following epidural morphine, as well as in other published reports, there was no clinical evidence for a supraspinal involvement in the mechanisms of this pain relief, since no opioid side effect nor vegetative depression (respiration, heart rate, blood pressure) were observed. This would strongly suggest that in the present work, at least for the initial 60 min, the pain-relieving action of epidural morphine can be explained by a depressant effect on spinal nociceptive transmission, directly at a spinal level. This is reinforced by another study that has shown that intravenous injections of low doses of morphine (0.05 mg/kg) did not modify either the lower-limb nociceptive reflexes or the associated sensation of pain, but, in contrast, were responsible for the classical opioid side effects in normal subjects. Thus, in the present study, even if the vascular absorption of epidural morphine occurred, pharmacokinetic data would indicate that blood levels would be very low (at least lower than 0.05 mg/kg) after a small 2-mg epidural morphine dose.

FIG. 6. Pooled data showing the depressive effects of epidural morphine on nociceptive responses elicited by a constant level of stimulus intensity. Each point represents the mean ± 1 SEM. Values are expressed in percentage of control values (as 100%). Open stars indicate the significance in the variations compared with the control values (paired t test). In the left lower part of the graph the regression curve equation with its significance is expressed (*** = P < 0.001). The onset of pain relief for all subjects is shown by the arrow in the middle of the graph.
Nevertheless, it would be interesting to repeat measurements of nociceptive reflex 4–6 h after epidural morphine, when pain relief is still present and blood levels are close to zero.

The last point that needs to be discussed concerns the possibility that epidural morphine could also exert a depressive effect on motor mechanisms in spinal cord. This idea is provided by some animal experiments that have shown a direct and specific excitatory effect of morphine on Renshaw cells when locally iontophoretically applied.21–23 Such a mechanism seems unlikely in our study, since we did not observe any significant change in the clinical features of the motor functions (e.g., muscle tone, tendon jerk reflexes, voluntary contraction, etc.) as regularly tested throughout each experimental session, before and after epidural morphine administration.

In conclusion, this study clearly suggests that the main mechanism of the pain-relieving effect of epidural morphine consists of a potent depressive effect on the transmission of nociceptive messages directly at a spinal level. Further experiments would be necessary in order to explore the selectivity of these depressive effects and to examine the hypothesis that epidural morphine produces "selective spinal analgesia" in humans.24

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