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Intrathecal Fentanyl Depresses Nociceptive Flexion Reflexes in Patients with Chronic Pain

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To investigate the selective role of intraspinal opioids on the perception and modulation of pain, seven subjects with chronic hip or back pain and one subject with C-6 quadriplegia received 25 μg of intrathecal fentanyl. The effect of lumbar intrathecal fentanyl on reported pain, nociceptive flexor withdrawal reflexes, a monosynaptic motor arc (H-reflex), and suprapinal effects such as miosis, nausea, respiratory depression was evaluated. In five of eight subjects the flexor withdrawal reflex was completely abolished within 15 min. In the others the reflex was significantly depressed from control values. Decreases in reported pain paralleled the decrease in the flexor reflex, H-reflexes remained unchanged, and no supraspinal side effects were observed. It is likely that these selective changes observed were from the isolated effect of fentanyl modulating nociception at the spinal cord level. (Key words: Anesthetics, intrathecal: fentanyl. Spinal cord: flexion reflexes; nociceptive reflexes.)

NUMEROUS STUDIES have reported the use of spinal opioids in the treatment of a variety of pain states.[1–10] Proposed advantages of spinal opioid analgesia include a selective blockade of pain pathways and lack of effect on sympathetic or motor activity.[11] Animal studies have suggested that morphine can selectively induce analgesia by the modulation of nociceptive input at the spinal cord level.[12–15],§ Parallel work examining the effects of opioids at the spinal cord in humans have demonstrated that morphine (0.2–0.3 mg/kg iv) had a depressive effect on lower limb nociceptive flexion reflexes in paraplegics.[16] In addition, 0.03–0.04 mg/kg of epidural morphine depressed the flexion withdrawal response in patients with acute postoperative pain.[17] In these patients the depression of the flexion reflex strongly correlated with the relief of postoperative pain. However, all patients had received an epidural blockade of 2% lidocaine 120–150 min prior to the injection of morphine, and it was unclear to what degree the spinal reflexes were depressed by prior administration of local anesthetic. Also, because the plasma pharmacokinetics of epidural morphine parallel those of an intramuscular injection,[18–20] there was concern over the possible effects of absorbed narcotic at the supraspinal level. The following study was undertaken to assess the spinal effects of narcotics on the nociceptive flexion reflex, by using a low dose of intrathecally administered fentanyl without prior local anesthetic injection and to relate these changes to a motor reflex arc, the H-reflex, and to the subject's perception of pain. The studied reflexes, the H and nociceptive flexion reflex, are represented in figures 1 and 2. They differ in that the H-reflex is a monosynaptic motor reflex (ankle jerk), while the nociceptive flexion reflex is multisynaptic with one or more interneurons completing the reflex arc.

Methods

After obtaining Human Subjects Committee approval and FDA permission to use fentanyl by the intrathecal route eight subjects (45–66 yr of age, mean 53.5 yr) were given diagnostic spinal blocks. Seven subjects had chronic back or hip pain and one subject had lower extremity spasticity secondary to traumatic C-6 quadriplegia. None of the subjects had received opioids for 24 h prior to the study, nor was any local anesthetic given prior to the study. In addition, all subjects had intact knee and ankle joint reflexes. Each subject received an intrathecal injection at the L2–3 level of 25 μg of fentanyl mixed with 0.5 ml of spinal fluid for a total of 1 ml. Prior to injection baseline pain assessments of the chronic pain condition were made with a rank pain scale (0 = no pain to 10 = excruciating pain).[21,22] These measurements were repeated at 5, 15, 30, and 60 min after the injection of fentanyl. In addition, comments on the level of discomfort from the electrical stimulus were noted. Sensory changes to pinprick, sensitivity to cold, pupil size, and respiratory rate were noted at similar intervals. Side effects such as nausea were also recorded.

The nociceptive flexion reflex[23] was elicited using bipolar surface electrodes (3-cm spacing) taped over the sural nerve behind the lateral malleolus (or posterior tibial nerve behind the medial malleolus, if a consistent response was not recorded from sural nerve stimulation). The stimulus consisted of paired 1.0 ms duration pulses, 2.0 ms apart, using a constant current stimulator. Stimuli were repeated no more frequently than every 20 s to avoid habituation. Nociceptive flexion reflexes were recorded from the biceps femoris and tibialis anterior muscles using surface electrodes (1.0-cm stainless steel discs) taped over

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§ Koll W, Haase J, Block G, Muhlberg B: The predilective action of small doses of morphine on nociceptive spinal reflexes of low spinal cats. Int J Pharmacol 2:57–65, 1963.

the muscle belly and tendon. Reflex threshold was established pre-injection as the lowest current intensity at which a muscle response was first detectable and consistently recorded using the staircase method.[24] Four nociceptive flexion reflexes were then recorded at a current intensity 1.5 times this threshold value, pre-injection and at 15 and 30 min postinjection. Amplitude (peak-to-peak) and latency (to onset) were then measured for the largest response at each time period.

Tibial H-reflexes were elicited with surface stimulating electrodes, the cathode in the popliteal fossa and the anode (3.0-cm stainless steel disc) medial to the patella. H-reflexes were recorded with surface electrodes (1.0-cm stainless steel discs) taped over the gastrocnemius-soleus muscle belly and the Achilles tendon. The active electrode over the muscle belly was positioned at a level 3-cm proximal to the midpoint from popliteal fossa to upper border of the medial malleolus on a line drawn from the mid-popliteal fossa to the Achilles tendon. Stimuli consisted of a 1.0-ms duration pulse from constant current stimulator at a frequency of less than 0.2 Hz to avoid habituation. Current intensity was gradually increased until a long-latency, presumed H-reflex was elicited; current intensity was then further increased until a short-latency M-response was observed and the long-latency response was abolished, consistent with an H-reflex. Current intensity was then reduced to elicit the largest H-reflexes observable and 5–8 such reflexes were recorded. This stimulation procedure was repeated at 15 and 30 min postinjection. Amplitude (peak-to-peak) and latency were measured for the largest response at each time period.

Statistical analysis of nociceptive flexor and H-reflexes were done with the Student's paired t test and the Wilcoxon rank sum test was used for analysis of the rank pain scale. $P < 0.05$ was considered statistically significant.

Results

In five of eight subjects the flexor withdrawal reflex was completely abolished within 15 min of intrathecal fentanyl administration, and in the other three subjects it was reduced in amplitude. The reflex amplitudes for the tibialis anterior and biceps femoris muscles at 15 and 30 min postinjection were significantly reduced from control values. Nociceptive reflexes of the tibialis anterior (mean ± 1 SE) expressed as a per cent of control were 13 ± 9% at 15 min and 14 ± 7% at 30 min after fentanyl injection. Values for biceps femoris at 15 min were 17 ± 11% and 12 ± 9% at 30 min. The changes in mean amplitude of both the tibialis anterior and biceps femoris at 15 and 30 min were statistically different from control data ($P < 0.01$). Mean values for the reported pain scale were 5.7 prior to fentanyl injection, 1.3 at 5 min, 0.8 at 15 min, and 0.4 at 30 min after fentanyl injection. These pain reports are significantly different from control values at all time intervals postinjection. In addition, all patients reported less discomfort from the electrical stimulus within 5 min of the fentanyl injection. The nociceptive

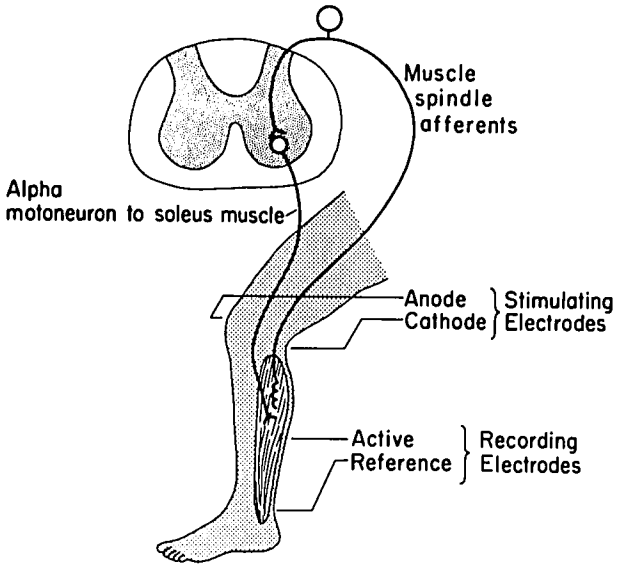

FIG. 1. The H-reflex, a one synapse, reflex pathway that is obtained by low-intensity current stimulation of large group Ia afferent fibers. The stimulus is applied over the posterior tibial nerve and the response monitored at the gastrocnemius-soleus muscle.

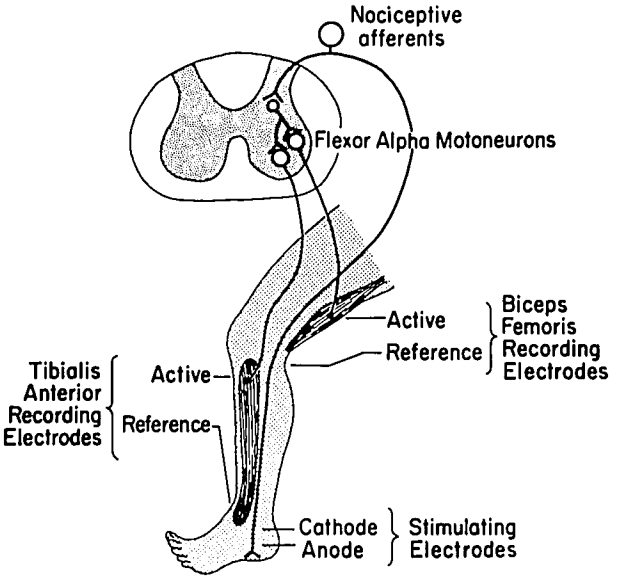

FIG. 2. The nociceptive flexion reflex. A strong electrical stimulus is applied over the posterior tibial nerve and the flexion response monitored over the tibialis anterior and biceps femoris muscles. The nociceptive flexion reflex differs from the H-reflex due to one or more interneurons in the spinal cord. These interneurons may have the ability to modulate the flexion reflex.

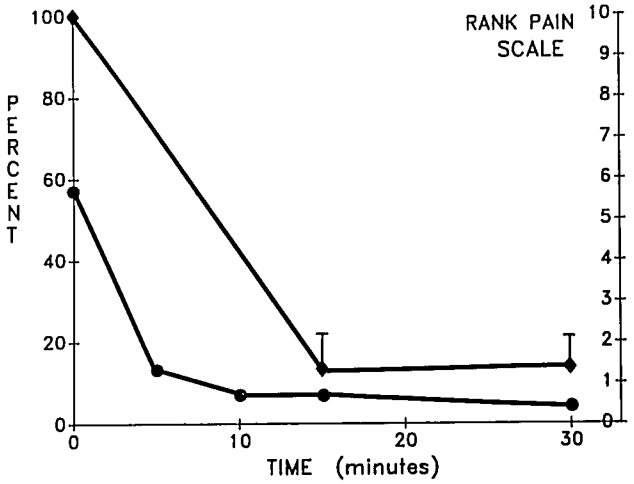

FIG. 3. Pooled data from tibialis anterior showing nociceptive flexor reflexes (♦) ±SE as a per cent of control values. Pooled rank pain scale (●) is also displayed. Time is expressed as minutes after fentanyl injection with T zero as control (n = 8).

reflexes expressed as a per cent of control and reported pain levels are shown in figures 3 and 4. Decreases in reported pain parallel the decrease in flexor withdrawal reflex. The amplitude and latency of the H-reflexes remained unchanged and are shown in table 1. In the patient with complete C6 quadriplegia with no preserved voluntary movement or light touch, vibration, or pin prick sensation in the lower extremities, a similar pattern of abolished nociceptive flexion reflexes but preserved tibial H-reflexes was observed after intrathecal fentanyl. In no subject was there any sensory changes to pin prick or temperature, and no subject had decreased pupil size, respiratory depression, or nausea.

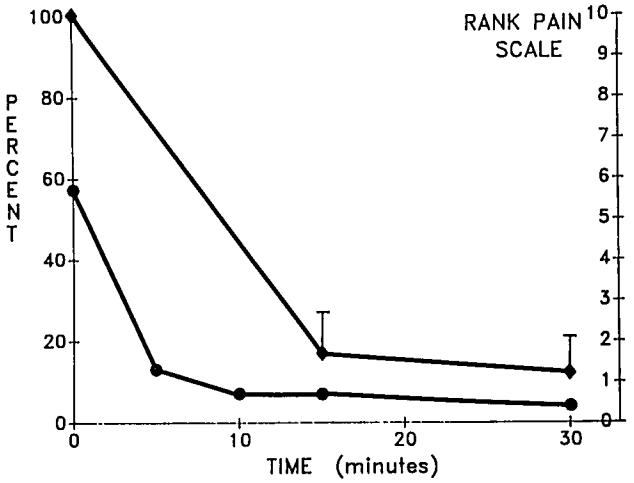

FIG. 4. Pooled data from biceps femoris showing nociceptive flexor reflexes (♦) ±SE as a per cent of control values. Pooled rank pain scale (●) is also displayed. Time is expressed as minutes after fentanyl injection with T zero as control (n = 8).

TABLE 1. H-Reflex Amplitude (mV) and Latency (ms) at Control and 15 and 30 Min Postfentanyl Injection

Subject	Control	15 Min*	30 min*
1 Amplitude	22.8	25.6	25.8
Latency	31.7	30.1	30.8
2 Amplitude	6.6	6.2	6.7
Latency	32.5	32.5	32.5
3 Amplitude	2.2	2.7	3.0
Latency	33.9	33.7	33.2
4 Amplitude	25	25	25.9
Latency	27.5	27.5	27
5 Amplitude	6.9	5.9	5.9
Latency	36.5	37.1	36.5
6 Amplitude	10.5	11.9	11.4
Latency	31.7	31.7	32.2

* Changes in mean amplitude and latency were not statistically different from control values.

Discussion

The ability of morphine to produce analgesia when injected into the spinal cord has been demonstrated in animals.[12–15] In humans previous studies using iv morphine in paraplegics[16] and epidural morphine in postoperative patients[17] have suggested that narcotics can also suppress nociceptive reflexes by selectively modulating input in the spinal cord. However, it was not possible to attribute the analgesic effects as having occurred solely on the basis of spinal cord modulation in the first study[16] because epidural morphine is well absorbed by the vascular system.[18–20] In the second study, epidural morphine suppressed nociceptive reflexes in patients with postoperative pain, but they had received 2% lidocaine epidural anesthesia 120 to 150 min prior to the morphine.[17] There is evidence that dilute concentrations of local anesthetics that fail to produce motor weakness when mixed with epidural narcotics can produce profound postoperative analgesia.[25–27,¶] Thus, epidural local anesthetic may have contributed to depression of nociceptive reflexes in this latter study. Because of this, it was decided to further investigate the ability of a spinally administered narcotic to selectively depress a nociceptive reflex and to correlate these changes with the subject's report of pain. In the present study because of the subarachnoid route of administration and the high lipid solubility of fentanyl (partition coefficient 813 *vs.* 1.42 for morphine), the effects of fentanyl should be largely limited to those at the local spinal cord level and not more rostral sites. In addition, the evidence from the complete quadriplegic subject fur-

¶ Youngstrom P, Eastwood D, Patel H, Bhatia R, Sutheimer C: Epidural fentanyl and bupivacaine in labor, a double-blind study (abstract). ANESTHESIOLOGY 61:A414, 1984.

ther demonstrated the effect of intrathecal fentanyl on an isolated section of spinal cord. The absence of myosis, sedation, or respiratory depression also supported the lack of effect at a supraspinal level.

In this study the close correlation between the decrease in the subject's reported chronic pain, discomfort from the electrical stimulus, and the depression of the nociceptive flexion reflex strongly suggests that narcotics can have a selective effect on the transmission of painful stimuli at the spinal cord level. Abolition of the nociceptive flexion reflex in a subject with complete quadriplegia by intrathecal fentanyl further suggests that the effect is spinal and not supraspinal. The tibial H-reflex, also recorded (eight in these patients), is a monosynaptic spinal reflex. Even with profound depression of the nociceptive flexion reflex and abatement of perceived pain, the H-reflex remained unchanged. The evidence from this study and others,[28,29] supports the concept that spinal opioids have a selective effect on input from A-delta and C-fibers while sparing spinal reflexes mediately by large-diameter I-A afferents.

In summary, this study has shown that intrathecal fentanyl strongly depresses the nociceptive lower extremity flexion reflex, and that these changes parallel the subject's report of pain. The monosynaptic H-reflex was unaffected by the fentanyl. It is likely that the selective changes observed were from the isolated effect of fentanyl modulating nociception at the spinal cord level.

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