Peripheral Opioid Analgesia in Teeth with Symptomatic Inflamed Pulps

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The purpose of this study was to investigate the ability of low-dose fentanyl to produce analgesia when administered via the periodontal ligament injection in teeth with symptomatic, inflamed pulps. All subjects presented for emergency treatment with moderate to severe pain and had a posterior tooth with a clinical diagnosis of irreversible pulpitis. Twenty subjects randomly received either 10 μg fentanyl citrate or saline placebo via the periodontal ligament injection in a double-blind manner. The subjects rated their pain prior to injection and rated pain intensity and pain half gone for 59 min postinjection. Low-dose fentanyl delivered via the periodontal ligament injection in inflamed teeth provided significantly greater analgesia than the saline placebo ($P < 0.05$). Since the dose of fentanyl used was less than the dose required to provide analgesia by a central mechanism, the results of this study may be consistent with a peripheral opioid mechanism of action.

Key Words: Pain; Opioids; Local analgesia; Inflamed pulps; Fentanyl.

Analgesia produced by opiates has classically been thought of as a centrally mediated phenomenon.[1] However, recent animal studies have shown that opiate receptors are present peripherally on primary afferent nerves[2-7] and that activation of these receptors can produce analgesia.[3-5,8-18] The mu-opiate receptor seems to be the most important receptor for antinociception,[19] and the majority of studies indicate that these receptors are located at the peripheral terminals of primary afferent nociceptive fibers.[2-7]

The mechanism of action of opiates upon antinociception is not known. It has been postulated that they may act by inhibiting or decreasing action potential propagation.[2,20] They may also inhibit the release of excitatory neuropeptides such as substance P from peripheral or central endings of the primary afferent fibers.[2,20] In a study by Levine and Taiwo,[19] opiates applied peripherally to rat paws decreased the hyperalgesia produced by PGE_2-induced inflammation. They concluded that opioids decrease the increased intracellular cAMP produced by PGE_2 via activation of inhibitory guanine regulatory proteins.

The majority of animal studies showing a peripheral antinociceptive effect of opioids are in inflamed-tissue models.[2,4,5,9,10,14,19] Studies on the antinociceptive effects of peripherally applied opiates in noninflamed-tissue models are contradictory.[3,8,21,22] Under normal conditions, an intact perineurium may act as a barrier to the effects of peripherally applied opiates.[18] It seems that inflammation plays an important role in the antinociceptive effects of peripherally applied opioids.[20]

Human studies relating to peripheral opiate analgesia deal mainly with chronic pain and acute postoperative pain management after perineural administration of morphine.[11-13,16] The results are varied, with reports of no analgesic effects in one study[23] and of prolonged analgesic effects in other studies.[11-13,16]

In an abstract by Hargreaves et al,[17] 0.5 mg of morphine sulfate administered via a periodontal ligament (PDL) injection in patients with acute apical periodontitis provided more pain relief than saline placebo administered via a PDL injection. They concluded that this was compatible with a peripheral site of action of opiate analgesia.

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The purpose of this study was to determine whether a periodontal ligament injection of fentanyl will provide analgesia in patients with inflamed pulps.

METHODS

Twenty adult subjects presenting for emergency treatment at The Ohio State University College of Dentistry were used in this study. All subjects were in good health as determined by a written health history and oral questioning. This study was approved by The Ohio State University Human Subjects Committee, and written consent was obtained from each subject.

Subjects had a posterior tooth with a clinical diagnosis of irreversible pulpitis and actively had moderate to severe pain associated with the tooth. By definition, these teeth were vital and gave a prolonged response to thermal testing. The teeth also had percussion sensitivity as well as a history of spontaneous pain and a widened periodontal ligament as determined by a periapical radiograph. No subjects had used a narcotic analgesic within 8 hr of the study, nor had they used a nonnarcotic analgesic with 4 hr of the study.

Twenty subjects were given a PDL injection of either 0.4 ml of saline placebo ($N = 10$) or 10 μg of fentanyl citrate ($N = 10$) in a double-blind manner. The solutions were placed in dental cartridges that were unlabeled except for a code number on the bag in which they were enclosed. The cartridges were prepared by removing the rubber plungers from the ends of standard anesthetic cartridges. The cartridges were emptied and washed, along with the rubber plungers, with soap and water using a nylon bristle brush inside the cartridge. The cartridges and rubber plungers were then rinsed three times with tap water and then with running tap water for 1 hr prior to being autoclaved. Using sterile technique, the saline placebo cartridges were made by placing 1.0 ml of 0.9% preservative-free sterile saline solution (Elkins-Sinn Inc., Cherry Hill, NJ) into the sterile cartridge using a 1.0-ml tuberculin syringe (Becton, Dickinson and Company, Rutherford, NJ). The fentanyl cartridges were prepared by drawing 0.50 ml of preservative-free fentanyl citrate 50 μg/ml (Elkins-Sinn Inc.) into a tuberculin syringe and placing it into a cartridge and then adding 0.50 ml of 0.9% preservative-free sterile saline to the same cartridge for a total concentration of 25.0 μg/ml. The two solutions were assigned a random five-digit code number from a random number table. The code number was unknown to the subjects and testing personnel. Two identical cartridges were prepared for each code number and placed into the bag containing the code number in case of cartridge breakage. If the solutions were not used by the end of the week, the solutions were discarded and new solutions were prepared. All injections were given by the principal investigator.

Prior to any injections, the subjects rated their pain on a scale from zero to three. Zero indicated no pain. One indicated mild pain, pain that was recognizable but not discomforting. Two indicated moderate pain, pain that was discomforting but bearable. Three indicated severe pain, pain that caused considerable discomfort and was difficult to bear. After injection, the subjects rated their pain using the scale above, and they also rated whether the "starting pain was at least half gone" on a nominal yes-or-no scale.

After baseline pain ratings were obtained, the coded test solution was administered via the PDL injection. The injection was made with a Septoject (DEPROCO Inc., Newcastle, DE) 30-gauge short needle in a calibrated Ligmaject syringe (Healthco, Inc., Boston, MA). The needle was inserted into the periodontal ligament at a 30° angle to the long axis of the tooth with the bevel directed away from the tooth until it could not be advanced any farther. A total of 0.4 ml of the test solution was administered under back-pressure via the PDL injection on the mesial (0.2 ml) and distal (0.2 ml) aspects of the tooth. If no back-pressure was encountered, the needle was repositioned until back-pressure was obtained. At no time was the experimenter or the subject aware of which solution was being injected.

The patients were questioned regarding their pain and whether the pain was half gone at 3 min postinjection and every 4 min thereafter. This continued for 59 min. Following completion of the study, either root canal therapy was initiated or the tooth was extracted.

The data from this study were collected and statistically analyzed. Pain intensity difference (PID) was determined by subtracting the pain intensity scores at each time interval from the baseline pain intensity for each subject. The sum pain intensity difference (SPID) was determined for each group by summing the mean PID scores at each time interval over the entire evaluation period (59 min). The sum of observations with pain half gone (SHLFGN) was determined by summing the number of "yes" responses at each time interval and dividing by the total number of subjects in the group. Initial pain, SPID, and SHLFGN were analyzed using independent *t*-tests with the outcome measures, SPID and SHLFGN, Bonferroni-adjusted. Values were considered significant if $P < 0.05$.

RESULTS

The fentanyl group consisted of 10 subjects. The mean age for this group was 28 yr, with a range of 20–39 yr. Two of the subjects (20%) were male, and eight of the

Table 1. Comparison of Values for Fentanyl and Saline Groups (Mean ± Standard Deviation)

Variable	*Fentanyl*	*Saline*
Initial pain	2.5 ± 0.5	2.4 ± 0.5
1-hr Sum pain intensity difference	21.9 ± 11.9	10.1 ± 9.1*
Sum of observations with pain half gone	10.0 ± 4.5	6.7 ± 5.21

* Statistically significant ($P < 0.05$).

subjects (80%) were female. The saline group consisted of 10 subjects. The mean age for this group was 30 yr, with a range of 21–41 yr. Six of the subjects (60%) were male, and four of the subjects (40%) were female.

The mean initial pain intensity of the fentanyl and saline groups are presented in Table 1. There was no significant difference between the initial pain intensities of the two groups.

Figure 1 shows the mean PIDs for the postinjection times. The mean PID for the fentanyl group was 1.46 ± 0.8, and for the saline group it was 0.67 ± 0.6. The 1-hr SPID for the fentanyl group was higher than that for the saline group and was significant. The SHLFGN for the fentanyl group was higher than that for the saline group. However, this difference was not significant.

DISCUSSION

All teeth used had a clinical diagnosis of irreversible pulpitis and spontaneous pain that was rated as moderate to severe in nature. Although studies by Seltzer et al[24] and Mendoza et al[25,26] indicate that clinical diagnosis cannot precisely predict the histological status of the pulp, severe and spontaneous pain appears to indicate severe pathosis of pulpal tissues. Mendoza et al[25,26] showed that teeth with a clinical diagnosis of irreversible pulpitis had moderate to severe changes of the nerves, vasculature, and connective tissues of the apical pulp tissue. Therefore, it is logical to assume that the pulps of these teeth were inflamed.

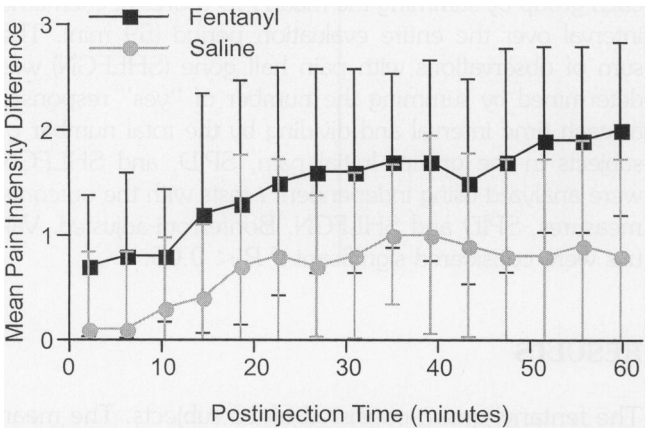

Figure 1. Mean pain intensity differences for the fentanyl and saline groups (bars represent standard deviations).

The majority of animal studies showing a peripheral antinociceptive effect of opioids are in inflamed-tissue models.[2,4,5,10,14,19] Joris et al[5] demonstrated peripheral opioid receptor mediated analgesia in rat paws with carrageenan induced inflammation. Russel et al[4] showed that opioids inhibited the spontaneous firing of afferent nerves in the knee joints of cats with kaolin and carrageenan induced inflammation. Stein et al[2,9,10] used Freund's adjuvant to induce inflammation in rat paws and demonstrated peripheral opioid mediated analgesia in these studies. Ferreira et al[14] demonstrated that morphine had a peripheral opioid receptor mediated analgesic effect on PGE_2-induced hyperalgesia in rats. Ferreira and Nakamura[27] have demonstrated that PGE_2-induced hyperalgesia is mediated by an increase in intracellular cAMP levels. Levine and Taiwo[19] also showed a peripheral opioid receptor mediated analgesic effect on PGE_2-induced hyperalgesia in rats and concluded that this was due to the ability of opioids to indirectly decrease the cAMP second messenger system in the primary afferent nociceptors. This may be similar to the inflammation seen in the dental pulp. Cohen et al[28] showed that teeth with a clinical diagnosis of irreversible pulpitis had a 25-fold increase in PGE_2 as compared to uninflamed pulps and theorized that this could explain the hyperalgesia associated with these teeth. An abstract by Hargreaves et al[17] reported an analgesic effect of low-dose morphine after PDL injection in endodontic patients with a clinical diagnosis of acute apical periodontitis. They concluded that this was consistent with a peripheral site of action for opiate-induced analgesia. Because inflammation seems to play an important role in the antinociceptive effects of peripherally applied opioids,[20] teeth with inflamed pulps were used in this study.

The mean initial pain intensities of 2.40 (saline group) and 2.50 (fentanyl group) correlated to pain which was discomforting but difficult to bear (between moderate and severe pain). This pain is representative of patients with irreversible pulpitis who presented for emergency treatment because they could not tolerate the pain any longer. Cooper[29] states that in order to obtain meaningful comparisons between the abilities of two drugs to provide pain relief, the pain experienced by the two groups should be the same. This criterion was met in this study,

since there was no significant differences in the starting pains of the two groups (Table 1). The severity of pain must also be standardized to obtain meaningful results. Just as the histological status of the pulp cannot be determined from clinical diagnosis,[24–26] patients with teeth that have inflammation of the pulp may present with varying degrees of pain.[25,26] In this study, only subjects who presented with moderate to severe pain were selected so that analgesia could be measured. According to Cooper,[29] if the pain is too mild, the active drug and placebo may both score equally high; whereas if the pain is too great, the active drug may not be able to produce any noticeable analgesia. Initial pain intensities that are too low may make the assay less sensitive to changes in pain intensity.[30] In this study, a starting pain of moderate to severe was used to ensure a starting pain with enough intensity to separate placebo effect from the effect of fentanyl while still allowing fentanyl to have an analgesic effect. Cooper[29] also states that if the pain is intermittent in nature, analgesia may not be attributable to drug efficacy. All subjects had constant, moderate to severe, spontaneous pain at the start of the study.

Figure 1 shows a comparison of mean PIDs for the fentanyl and saline groups. The mean PID for the fentanyl group was 1.46 ± 0.8. This represents an overall change in initial pain intensity from moderate-to-severe to mild. The mean PID for the saline group was 0.673 ± 0.6. This represents an overall change in initial pain intensity from moderate-to-severe to moderate. The 1-hr SPID (Table 1) revealed that the difference between the fentanyl group and the saline group was significant, showing that the subjects in the fentanyl group had significantly greater analgesia than the subjects in the saline group during the 59 min studied. Therefore, the periodontal ligament injection of fentanyl produced analgesia that may be consistent with a peripheral opioid-mediated mechanism.

The SHLFGN for the fentanyl group was higher than that for the saline group. However, this difference was not statistically significant. The finding that the SHLFGN did not show a significantly higher score for fentanyl than for saline may indicate that this measure was not as sensitive as the PID for this study. The SHLFGN score will not record a decrease in pain intensity other than the subject's perception that it is at least half gone. Therefore, the greater pain relief achieved by fentanyl was not detected with this measure.

Figure 1 shows that the analgesic effects of both the fentanyl and saline groups behaved similarly over time. This is consistent with a placebo effect, since therapeutic responses to placebos and to active agents may resemble each other in magnitude and duration.[1,8] However, the fentanyl group provided a greater amount of analgesia.

The PDL injection was the route of drug administration. Fuhs et al,[31] Smith and Walton,[32] and Dreyer et al[33] have shown that the PDL injection caused the injected fluid to enter the marrow spaces of the alveolar process and reach the apical foramen of the injected teeth. Therefore, this injection technique is capable of delivering solution to the peripheral portion of the nerve. Smith and Pashley[34] have shown that the PDL injection of epinephrine containing anesthetic solutions causes systemic changes (increases in heart rate). While there is an initial systemic effect due to the epinephrine, the anesthetic solution injected does result in pulpal anesthesia.[35,36] If this were an intravenous injection, little or no anesthetic effect would be demonstrated. Therefore, the periodontal ligament injection should not be viewed as an intravenous injection.

Would the uptake of fentanyl administered via the PDL injection result in plasma levels high enough to produce a central effect? The normal dose of fentanyl for preoperative medication, as an adjunct to regional anesthesia, or to control postoperative pain is 50–100 μg intramuscularly or by slow intravenous injection.[37] Gourlay et al[38] measured the fentanyl–analgesic response relationship in the treatment of postoperative pain. Thirty surgical patients received fentanyl via a patient-controlled system. They found that the hourly postoperative dose of fentanyl for pain control was initially high, 100–140 μg/hr for the first 5 hr, and then decreased to 40–60 μg/hr for the next 30 hr. The initially high levels of fentanyl are consistent with loading doses necessary to achieve an analgesic blood and brain concentration. Hill et al[39] used electrical dental stimulation and measured subject pain reports to evaluate the concentration–effect relationships of fentanyl. Plasma levels were achieved through computer-controlled infusions. A 50% decrease in pain intensity was reported for a fentanyl plasma concentration of 1.6 ng/ml. Similar plasma-concentration-related effects were seen following a 4μg/kg intravenous bolus of fentanyl. Bower and Hull[40] found an intravenous bolus of approximately 170 μg of fentanyl resulted in an initial plasma concentration of approximately 3 ng/ml, which rapidly decreased to approximately 0.2 ng/ml by 30 min. These studies indicate that the low dose of fentanyl used in this study (10 μg) would be insufficient to produce the plasma concentrations necessary to provide analgesia by a central mechanism.

CONCLUSION

Low-dose fentanyl delivered via the PDL injection in inflamed teeth provided significantly greater analgesia than the saline placebo. Since the dose of fentanyl used was less than the dose required to provide analgesia by a cen-

tral mechanism, the results of this study may be consistent with a peripheral opioid mechanism of action.

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