Change in Pain Threshold by Meperidine, Naproxen Sodium, and Acetaminophen as Determined by Electric Pulp Testing

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The purpose of this study was to compare changes in pain threshold caused by meperidine, naproxen sodium, acetaminophen, and placebo. The change in pain threshold was measured by electric pulp testing. Acetaminophen elevated the pain threshold statistically significantly. Clinically, however, the superiority of acetaminophen is questionable. No elevation of the pain threshold occurred with narcotic drugs or with nonsteroidal anti-inflammatory drugs: our research shows that the electric pulp tests of patients who have taken these drugs preoperatively will have results similar to those of patients who have taken no drugs. We question the philosophy of administering these drugs for change in pain threshold at the levels used here preoperatively.

Key Words: Meperidine; Naproxen; Acetaminophen; Pain threshold; Dental pulp testing.

Many practitioners believe that narcotics raise the pain threshold for all types of pain. Narcotics are frequently administered with the intention of reducing interoperative pain perception. There is new evidence that narcotics are minimally effective in reducing sharp pain, such as the pain caused by needle penetration or by incision.

In 1986, Cooper, Vierck and Yeomans¹ trained subjects to discriminate sharp pain, which they called first pain, from the dull pain that occurred slightly after sharp pain from brief thermal or electric skin stimulation. They found that 5 or 10 mg of systemic morphine raised the threshold for the dull or second pain without changing the initial sharp pain perception. They concluded that opioid receptors were lacking on the myelinated A neurons, which send nerve impulses faster than their unmyelinated counterparts, the C neurons, which are usually associated with dull pain transmission. Other researchers found that the sharp pain threshold for electric skin stimulus was unchanged by aspirin, acetaminophen, or codeine.²

Edwall and Olgart³ found human dental pulp to be an excellent model for pain study because pulp transmits only pain signals, regardless of stimulus. Research by Dong and his group⁴ has found a few mechanoreceptors in cat dental pulp, but the role of these receptors is not clear. Human dental pulp continues to be generally regarded as the ideal organ for study of pain. Using this almost pure pain test bed, Taddese and coworkers⁵ dyed labeled nerves in the dental pulp to identify them in the semilunar ganglion. They found a paucity of opioid binding sites in myelinated, large-diameter neurons. The majority of these receptors were found on unmyelinated C fibers. By using a strain of mice genetically lacking the µ opioid receptor, Matthes and others found that the clinical effect of morphine was localized almost exclusively on the µ opioid receptor.⁶ The µ receptor-deficient animals showed no change in pain threshold or in behavior following opioid dosing, and these mice showed no evidence of addiction.

Other pain control drug receptors exist within the nervous system. Acetaminophen apparently affects specific receptors, although these receptors are not yet well...
defined. Unusual central nervous system activity was observed when Piletta and others used acetaminophen to elevate the pain threshold for electric stimulation of the skin; no such effect was observed when aspirin was used.7

Other investigators have found evidence that salicylates and nonsteroidal anti-inflammatory drugs act centrally, a finding that contrasts with the classic thinking that the action of these drugs is peripheral.8 After administering aspirin, these researchers found an elevation of the pain threshold as measured by a dental pulp tester, using only a single-intensity stimulus. Bannwarth and coworkers9 reviewed 65 studies that found interactions between neurotransmitters and prostaglandins, suggesting a link between central and peripheral mechanisms. They further note that the classic prostaglandin mechanism of decreasing cyclooxygenase also occurs within the central nervous system. Sandrini and others10 found that ibuprofen raises the threshold for pain-induced reflex, suggesting a central pathway of action. Gershman and Giebartowski11 noted that electronic dental anesthesia raised the pain threshold for electric pulp testing.

As early as 1963, Mumford12 suggested dental electric pulp testing as a means of comparing pain-relieving drugs. He also noted that painful pulpal inflammation alters mechanical and thermal stimulation thresholds, whereas the electric stimulation pain threshold was not reliably different under these circumstances.13

A pilot study by the third author, using 1.5 mg/kg of parenteral meperidine, showed no increase in the sharp pain threshold, as measured by electric pulp tests. The present study uses electric pulp testing to compare changes in pain threshold effected by meperidine, acetaminophen, naproxen sodium, and placebo.

METHODS

After we received the approval of the human studies committee, we accepted and obtained consent from 80 subjects from the dental emergency clinic. The patients, whose chief complaint was moderate to severe dental pain, had to meet several criteria. We required that subjects be between the ages of 18 and 60, weighing between 110 and 180 pounds. To be considered, subjects could not have had any meal within the previous 3 hr or any analgesics within the previous 12 hr. Subjects could not have a history of allergies to any of the test drugs or a history of addiction to narcotics or alcohol. Female subjects could not be pregnant, as proven by pregnancy test or history of surgical sterilization. Subjects could not have had monoamine oxidase inhibitors within the last 14 days. No subjects with heart pace-makers were allowed, and subjects had to have a minimum of seven teeth opposite the painful side without deep restoration, caries, or history of trauma.

Patients were blindly assigned by prior drawing to one of 4 groups of 20. Group 1 participants were given 220 mg of naproxen sodium (Aleve®). Group 2 participants were given a placebo capsule (Cebocap®). Group 3 received 100 mg of meperidine (Demerol®), and group 4 was given 1000 mg of acetaminophen (Tylenol®). Drugs were administered by a nontesting investigator. Drugs were not disguised beyond being given in an opaque cup. Neither the subject nor the investigator administering the electric pulp tests knew what drug had been given. All tests were administered by one of the first two authors.

Patients were not compensated. The only rewards were the possibility of receiving a drug that might make treatment less painful and the prospect of aiding others.

A single Model 2006, Analytic Technology (Redmond, WA) was used for all tests, according to manufacturer's instructions. Voltage was reproducible, corresponding to the 0–80 numerical scale on the digital display. The Model 2006 produces an increasing voltage square wave that is delivered in 10-pulse bursts, reaching a maximum of 350 V at 2 Ω at full scale (80 on the digital display scale). Rate of increase was set to “4” to allow accurate determination of first perception of stimulus. The calibration is such that 100 V is reached at a scale value of 35–40. The area to be tested was isolated with cotton rolls, and the toothpaste-coated electrode was placed on the middle of the buccal surface of the natural crown of the tooth to be tested. Six teeth were to be tested; a tooth not among these six teeth was used to introduce the patient to the test procedure. A test was conducted on each of the six asymptomatic teeth with unrestored buccal surface that were not on the side with the painful tooth. Patients were asked to stop the test either by releasing their hold on a metal clip connected by wire to the tester handle or by signaling with a raised hand when they first felt a definite stimulation from the test machine, as demonstrated during the introductory test. After drug administration, patients were seated in a waiting area for 45 min to allow drug absorption, after which they were taken back to the same room, where the pulp tests were repeated on the same teeth in exactly the same manner.

Descriptive measures were obtained so that means and standard deviations could be reported for the time 1 and time 2 readings. A paired t-test was used to compare the readings at time 1 and at time 2 for the four groups.

Since no treatment was administered prior to obtaining the time 1 scores, these scores were considered as a covariate in the study design, and analysis of covari-
ance was used to compare the time 2 scores of the four groups. By using analysis of covariance, the effect of the covariate was removed from the error term, thereby increasing the power of the F-test to detect differences among the four groups when comparing the adjusted time 2 scores.

RESULTS

The means and standard deviations of all tested teeth in each of the four groups are shown in Table 1. A comparison of the time 1 and time 2 means individually for each group shows that the difference for acetaminophen is statistically significant ($P < 0.01$). None of the comparisons involving the other three drugs was statistically significant (see Table 1). However, even though the comparison for acetaminophen was statistically significant, this difference is probably not clinically meaningful with an average test result of 4 units higher on the 80-unit scale.

The results of the analysis of covariance revealed no statistically significant differences among the four groups when comparing the adjusted time 2 scores.

DISCUSSION

Some dental diagnostic tests have only questionable validity when the patient has taken a pain reliever before the examination. If a pain threshold is drug-altered, comparisons at different times become clouded by all of the variables affecting drug concentration.

In cold water-induced pain tests comparing morphine to ibuprofen, researchers learned that morphine allowed subjects to hold their arm in cold water longer, while ibuprofen’s effect was no different from the effect of placebo. However, the results of the present study indicate that electric pulp tests are affected little, if any, by the three drugs tested.

A model electric pulp tester used in an earlier study gave inconsistent results because of variation between voltage output and numerical readout. This was not a problem with the machine used in the current study because of technological advances. Yet contemporary studies, such as work by Lado et al, find large variations between readings on the same individual with repeated tests, in spite of the use of a highly reproducible stimulus from the same type of machine used in this study. In contrast, Vreeland et al found no significant differences between baseline electric pulp test readings from one week to the next.

The 45-min waiting period was chosen from clinical observations that a drug’s effect on pain can generally be seen within 30 min following administration. A longer waiting period may have resulted in poorer patient participation because of deferred treatment for the painful tooth. We wished to avoid administration of any other drugs, even local anesthetic administered contralaterally, because systemic action may be a factor in changing test results. Furthermore, the half-life of the shortest-acting drug in the study, acetaminophen, is about 2 hr, and a longer wait might result in decreasing drug levels in some individuals.

Threshold elevation with acetaminophen suggests that preoperative use of this drug may make painful treatment easier for certain patients who demonstrate particular susceptibility. However, susceptible individuals would be difficult to identify. A history of effective pain relief with acetaminophen may be one method of identifying patients who would benefit. Pain threshold determination with electric pulp testing as described in this study would be neither efficient nor feasible for patient screening. Additionally, diagnostic electric pulp test results for patients taking acetaminophen may be suspect. This underscores the necessity of using control teeth, and not relying on prior test data unless pretest drug experience is consistent.

In that electric pulp tests stimulate sharp pain, this study supports the assumption of Cooper et al that there is a difference between sharp pain and dull pain analgesia, and that sharp pain is not significantly altered by opiates. This study also confirms the observation by Taddese et al that the sharp pain of a pinprick is not modified by opiates. Further, we find that at usual doses, nonsteroidal anti-inflammatory drugs and acetamino-
phen are not particularly effective at changing the threshold to sharp pain.

REFERENCES