A Pilot Study Comparing Ketoprofen and Acetaminophen with Hydrocodone for the Relief of Postoperative Periodontal Discomfort

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The aim of this study was to compare ketoprofen to acetaminophen with hydrocodone (A/H) in a postoperative periodontal pain model. A double-blind protocol was used. Thirty minutes prior to each procedure, subjects were given orally either 100 mg ketoprofen or a placebo tablet. Four hours later, the subjects took either 50 mg ketoprofen (ketoprofen group) or 1000 mg acetaminophen with 10 mg hydrocodone (placebo group). Subjects reported levels of overall discomfort and pain using visual analog scales at eight hourly intervals following the first dose of ketoprofen or placebo. Information about adverse side effects was requested from the patients in the form of a checklist. The results revealed only small differences between the two drug regimens with respect to levels of pain or overall discomfort. A/H provided significantly better pain relief at Hours 5 and 6, while overall discomfort levels were significantly higher with ketoprofen than with placebo at Hours 3 and 4. Pain levels were low for both groups. It is recommended that additional analgesics for mild to moderate pain should be tested.

Key Words: Dental analgesia postoperative dental pain, Nonsteroidal anti-inflammatory drugs, Ketoprofen, Hydrocodone, Acetaminophen.

Dental practitioners traditionally have prescribed a variety of drugs for controlling postoperative dental pain.[1] These have ranged from aspirin or acetaminophen for mild pain to combinations of drugs such as acetaminophen or aspirin with codeine or hydrocodone for moderate pain, or with oxycodone for the most severe dental pain. Caution is required when prescribing opiates because they are highly habit forming, frequently cause nausea and constipation, and produce respiratory depression, somnolence, and hypotension.[2] Recently, nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin have been studied as analgesics in dentistry. Dionne et al[3] have stated that newer NSAIDs are more effective than traditional analgesics and display fewer adverse side effects than aspirin and opiates. Ketoprofen has been used in several dental studies and was found to be an effective analgesic.[4–7] A review of the literature shows only one report of ketoprofen using periodontal surgery as the pain model.[8] In that study, ketoprofen relieved pain better than either aspirin or a placebo.

Ketoprofen, a phenylproprionic acid derivative, is one of the newer nonsteroidal anti-inflammatory drugs.[9] It was originally synthesized in Paris in 1967, 3 yr after ibuprofen, and FDA approval was granted in the United States in January 1986.[10] Ketoprofen has analgesic, anti-inflammatory, and antipyretic properties.[10] Adverse reactions are generally similar but less intense than other NSAIDs. The most common adverse reactions reported by patients are gastrointestinal irritation, edema, and transient depression of renal function, all of which are reversible with discontinuation of the drug.[9,10] Like other NSAIDs, ketoprofen inhibits the cyclooxygenase

Received August 20, 1995; accepted for publication May 15, 1997.
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Anesth Prog 44:49–54 1997

ISSN 0003-3006/97/$9.50
SSDI 0003-3006(97)

pathway of arachidonic acid metabolism.[10–17] Additionally, ketoprofen appears to inhibit leukotriene production through the blockage of the lipoxygenase pathway, may possess antibradykinin activity, and produces membrane stabilization.[10] Ketoprofen is rapidly absorbed from the gastrointestinal tract, is 99% bound to plasma proteins, and is conjugated in the liver. It is excreted as a glucuronide primarily in the urine.[18] Ketoprofen was used in this study for a number of reasons. It is an effective analgesic with minimal side effects compared to other NSAIDs and combination drugs. The FDA has approved it for use as an analgesic in situations of mild to moderate pain, and it is readily available in the US[10,15,16,18] This study was designed to compare the effectiveness of ketoprofen with that of an established dental analgesic combination when these agents are given in their typical manner for treatment following periodontal surgery.

METHODS

A total of seven surgical procedures were performed on five different subjects, yielding 112 data points. The subjects selected for this study were ASA I or II and were not taking analgesics or any medications that might adversely interact with either the local anesthetic or the analgesics given. Subjects had been treated at Oregon Health Sciences University (OHSU) dental school for varying periods of time with nonsurgical periodontal therapy. All subjects participated with informed consent, and this study was approved by the Committee on Human Research at OHSU. All subjects received a presurgical evaluation by one of the authors (KR). All subjects had received oral hygiene instructions during the previous treatment and were root planed at least 6 wk before the surgery.

Subjects were given either a lactose-based placebo tablet (Consolidated Midland Corp., New York, NY) or 100 mg ketoprofen (Orudis, Wyeth-Ayerst, Philadelphia, PA) ½ hr before the beginning of their surgery, and received instructions on usage of the visual analog scale and the reporting form (Figure 1). The pretreatment medication was chosen in a random manner, and the type of medication was not disclosed to the operator or subject. All surgeries were completed by the same surgeon (KR). The surgical procedures were similar for all subjects and were nearly identical within a given subject. After application of a topical anesthetic, 1.8 ml of 3% mepivacaine was given as a block injection for the surgical site. Additionally, up to 1.8 ml of 2% lidocaine with epinephrine 1:50,000 was utilized for hemostasis and as soft tissue infiltration anesthesia. The periodontal surgery was then performed using an inverse bevel incision of the gingiva, reflection of a full thickness mucoperiosteal flap, wound debridement, scaling and root planing, osseous surgery where indicated, apical positioning of the flap, and suturing with 4-0 silk sutures.

Some patients were treated with occlusive membranes (Gore-Tex, Flagstaff, AZ) or various types of bone augmentation material (Interpore, Irvine, CA; Mile High Bone, Denver, CO).

After the surgery, the subjects were given 16 oz of a 0.12% chlorhexidine digluconate mouth rinse (Peridex, Proctor & Gamble, Cincinnati, OH) and a supply of either ketoprofen 50 mg, if they were pretreated with ketoprofen, or acetaminophen 500 mg with hydrocodone 5 mg (Lortab, Russ Pharmaceuticals, Hobart, NY) (A/H), if pretreated with placebo. The subjects were instructed to place marks hourly on a 100-mm vertical line to indicate the degree of pain they were experiencing (Figure 1). Each 1 mm on the scale equaled one unit of pain or overall discomfort in the data analysis. The bottom of the scale denoted no pain at all, while the top was the worst pain imaginable. Additionally, subjects marked a similar line indicating their degree of overall discomfort (no discomfort to extreme discomfort).

Overall discomfort levels were recorded in an attempt to consider the general overall feeling—for instance, irritability, sluggishness, restlessness, anxiety, etc. Four hours after the first pills were given, the subjects were instructed to take a second dose of medication dispensed earlier. They were informed that they could take their second dose earlier than indicated if their pain became unbearable, but none chose this option. The subjects were told they could take further medication as needed after the eighth hourly report was recorded. Those subjects undergoing the A/H regimen were given a placebo initially and received their first dose of A/H after the fourth hourly report. A report was made of the number of pills taken, and the subject was asked to report any side effects experienced.

A postoperative appointment was scheduled for 1 wk after the surgery to remove sutures and collect the reporting forms. A 3-wk postoperative appointment was also scheduled to follow the course of the healing.

Inter- and intragroup data were analyzed by the Mann-Whitney *U*-test with $P \leq 0.05$.

RESULTS

One subject was disqualified and data points disregarded because of reporting inconsistencies that suggested the patient did not fully understand the visual analog scale rating process.

Figure 2 illustrates average pain scores for the 40 data points contributed by the two subjects treated with

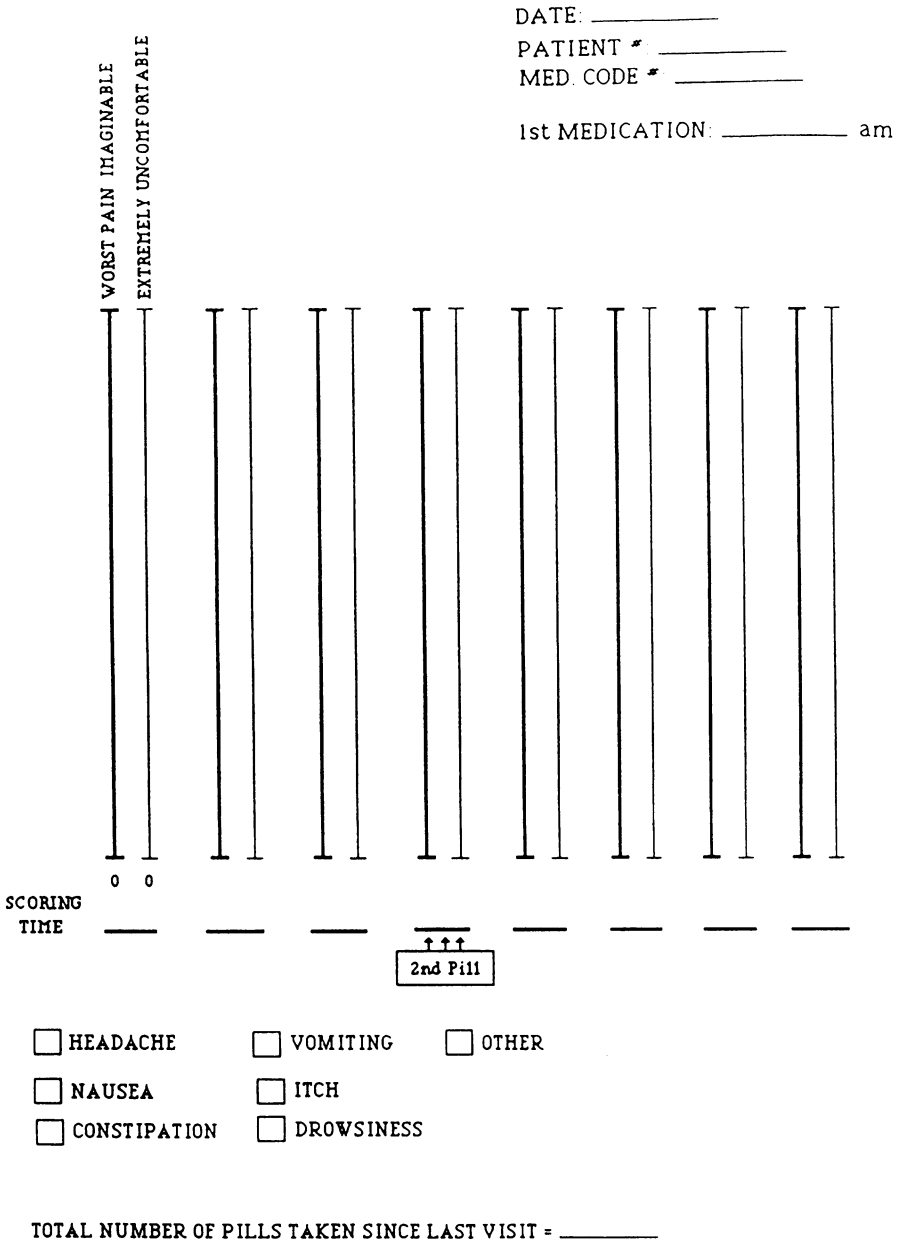

Figure 1. Visual analog scale given to subjects. This is a 100-mm scale where subjects were asked to grade levels of pain and overall discomfort at hourly intervals.

ketoprofen and the three subjects treated with placebo followed by A/H. Initial pain scores for both groups were very low, as expected, since they were reported just 30 min after the administration of local anesthesia. As the nerve block began to wane, pain scores began to rise. For the placebo group, this rise was very rapid from the first to the second hour. From an Hour 1 score of < 1, the average pain score rose dramatically to 12 at Hour 2, with no further increase over the next two scoring intervals. This increase, however, was not statistically significant utilizing the Mann-Whitney *U*-test with $P \leq 0.05$. The only statistically significant differences in pain scores between the groups were at Hours 5 and 6. At these time intervals, A/H proved to be superior to ketoprofen for pain relief.

Figure 3 illustrates average overall discomfort scores for the 40 data points contributed by the subjects. There was a small but steady increase in overall discomfort in the placebo group during the first phase of the study (first 4 hr). By Hour 5, the overall discomfort rose dramatically over the Hour 4 recording, and this corresponds to the first administration of A/H. At the remaining recordings, the level of overall discomfort decreased for the A/H group. For ketoprofen, overall dis-

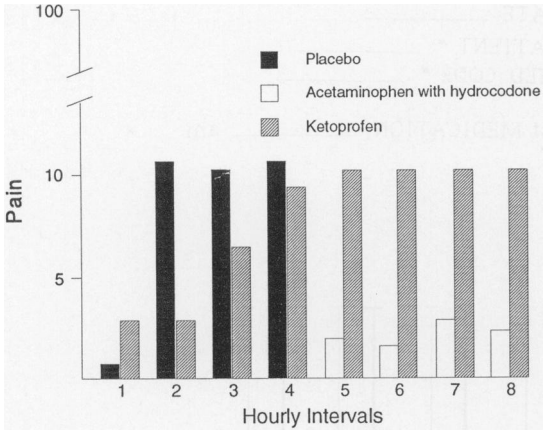

Figure 2. Mean pain levels reported by subjects in each group. Note that subjects originally given a placebo received acetaminophen with hydrocodone after the fourth hour. Significant intergroup differences were noted only between Hours 5 and 6.

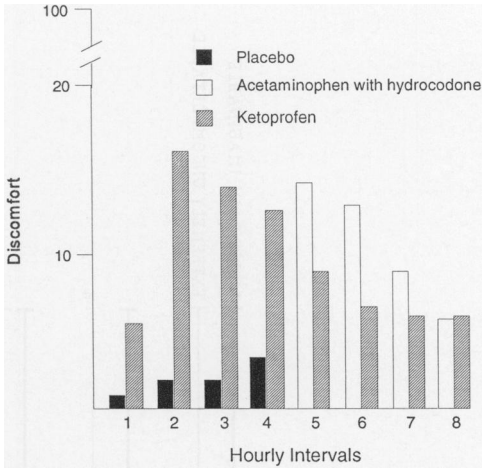

Figure 3. Mean overall discomfort levels reported by subjects. Note that subjects initially given a placebo were given acetaminophen with hydrocodone after the fourth hour. Significant intergroup differences were noted only at Hours 3 and 4.

comfort reached a maximum at Hour 2 and then dropped each hour for the duration of the study. Subjects taking ketoprofen experienced significantly more overall discomfort at Hours 3 and 4 than those administered the placebo ($P \leq 0.05$). There were no statistically significant differences in overall discomfort between the ketoprofen and the A/H medications.

Subjects given ketoprofen took an average of six-and-one-half tablets (not including the two given preoperatively), while subjects given acetaminophen with hydrocodone used an average of six tablets each. This difference was not statistically significant.

There were a total of six boxes available for checking side effects experienced, as well as an additional box for writing in side effects experienced but not listed (Figure 1). The only side effect checked by any subject was drowsiness. This box was checked by all subjects in both groups. Additionally, one subject in the A/H group related heaviness in the ears and dizziness.

DISCUSSION

Opioid analgesics are generally used in dentistry to control moderate to severe pain. The literature suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) are equally effective analgesics as opioids and have the additional advantage of fewer adverse side effects.[19–21] The oral surgery pain model involving third molar removal has been well documented, but periodontal pain may be expected to be qualitatively different.[22] Primary closure is generally obtained after periodontal flap surgery, and most of the trauma is limited to soft tissue. In contrast, third molar removal generally involves manipulation of significant amounts of bone and frequently primary closure is not obtainable.[22] Until now, a periodontal pain model has not been developed, even though there is a need for these types of data due to the increasing number of periodontal surgery procedures being performed. There has been only one study on postsurgical periodontal pain relief by ketoprofen, but it is difficult to interpret because the comparator drug, aspirin, was not administered at its ceiling analgesic dose.[8] Ketoprofen is an orally effective dental analgesic at a dose of 50 mg, while acetaminophen and hydrocodone are maximally effective analgesics at doses of 1000 mg and 10 mg, respectively.[1–10,17] The purpose of this study was to compare ketoprofen to acetaminophen with hydrocodone at their ceiling analgesic doses in a periodontal pain model, where the dosing regimen approximates that used in clinical practice. Flath et al[23] have recommended a loading dose of NSAIDs when they are to be used postoperatively. Opiate combinations generally are not used in the same manner.

A/H appears to be a better analgesic in this pain model. Ketoprofen, while not statistically different from placebo in pain relief, was associated with more overall discomfort than the placebo. The low number of subjects in each group must be considered when interpreting these data. The ultimate clinical question that must be asked is, "Does this periodontal model involve enough pain to be useful for analgesic testing"? Total pain levels were low as reported by subjects on a visual analog scale. The highest pain level reported by any subject was 29, and the average pain level of all subjects at all recordings was 7.15 on a scale of 0 to 100. Pain levels reported here are generally mild to moderate. Other mild to moderate drug regimens should be eval-

uated to determine their appropriateness for this type of surgical procedure.

It is difficult to find patients with bilaterally symmetrical periodontal disease. Smith et al[24] screened a sample of over 1500 patients to find 12 with comparable marginal periodontal destruction. If a large enough sample can be obtained, the split mouth design would prove most useful in data analysis.[25] If the number of subjects in each group were greater than in this study, statistically significant differences between the groups might be reached at more of the hourly recordings.

Upon examination of the data, the Mann-Whitney *U*-test seemed most appropriate. This is a nonparametric test that is based on a ranking system. The problem with this test occurs when there are a number of ties within the rankings. Of the 80 data points gathered, subjects reported 0 (on a 100-mm scale) 28 times. This led to a number of ties within the rankings, and as the number of ties between groups increases, there is a tendency to be too conservative; that is, there is a greater possibility of failing to reject a null hypothesis that should have been rejected.[26]

CONCLUSION

In conclusion, we have demonstrated that at certain postoperative time intervals subjects report less pain with the administration of acetaminophen with hydrocodone than with ketoprofen. In addition, subjects report more overall discomfort postoperatively in response to ketoprofen than to a placebo. All other comparisons may or may not be relevant, and it is suggested that a similar study with more subjects ought to be undertaken.

ACKNOWLEDGMENTS

The authors thank David R. Homma and Wyeth Pharmaceutical for their generous gift of Orudis; John Roberts and Russ Pharmaceutical for supplying the Lortab; and Dennis Muir and Proctor & Gamble for supplying the Peridex used in this study. This research was supported by a Basic Research Sciences Grant awarded to Oregon Health Sciences University School of Dentistry.

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