Naproxen Sodium: Comparative Efficacy and Tolerability of Two Dosages for Pain After Joint Surgery

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ABSTRACT: In a multicenter, randomized, double-blind, parallel trial, the efficacy and tolerability of two regimens of naproxen sodium were compared in a two-day treatment of moderate to severe pain following open surgery of the hip, shoulder, knee, and ankle joints. Of 147 patients enrolled, the data of 99 were valid for efficacy analysis, 45 in the low-dose regimen (day 1, 1,100 mg; day 2, 2,825 mg) and 54 in the high-dose regimen (1,650 mg/day). At 12 interviews each day, patients evaluated intensity of pain using numerical scales and recorded complaints. At the end of the study, overall efficacy was evaluated. Although there were no statistically significant differences between the two regimens for efficacy or tolerability, the high-dose regimen achieved greater pain relief in patients who had hip or shoulder surgery, suggesting that this regimen had greater cumulative efficacy for these patients.

Introduction

Naproxen sodium is a potent and rapidly absorbed analgesic and anti-inflammatory agent. The analgesic potency of naproxen sodium has been demonstrated in controlled clinical trials in the treatment of moderate and severe postoperative, musculoskeletal, and postpartum pain, and in dysmenorrhea. In patients with postoperative pain, the drug has been shown to provide greater pain relief at standard dosages than acetaminophen and oral pentazocine, to be at least as effective as acetaminophen plus codeine, and to outperform an intramuscular 10 mg injection of morphine sulphate. After arthroscopic meniscectomy, patients using naproxen sodium not only experienced less pain than those taking placebo, but also had less synovitis and effusion, a more rapid return of movement and quadriceps function, and a faster return to activity. For pain following major gynecological surgery, naproxen sodium proved equal in efficacy and superior in tolerability to a combination of aspirin, phenacetin, caffeine, and codeine phosphate. Following various orthopedic surgical procedures, a single 600 mg dose (equivalent to naproxen sodium 660 mg) of naproxen (the parent acid of naproxen sodium) was a more effective analgesic than a 400 mg dose of naproxen (equivalent to 440 mg naproxen sodium). Both doses were more effective than a single dose of propoxyphene 65 mg. Naproxen was an efficacious pain reliever after open surgery of the knee and foot, reducing the need for narcotic analgesics. In the relief of postoperative pain, 400 mg of naproxen outperformed 25 mg and 75 mg of meperidine.

The purpose of this study was to compare the efficacy and tolerability of a high-dosage regimen of naproxen sodium (1,650 mg/day for two days) with those of a low-dosage regimen (1,100 mg/day 1 and 825 mg day 2) in patients with moderate to severe
pain following open joint surgery of the hip, shoulder, knee, or ankle. The design of this multicenter study was double-blind, randomized, and parallel treatment with the two regimens.

**Materials and Methods**

**Patient Selection**

Patients who qualified for this trial were of legal age and had moderate to severe pain warranting oral analgesic medication. At the start of the study, or baseline, patients were enrolled no more than 48 hours after surgery, had not taken oral or parenteral narcotics or other analgesics for at least 4 hours, and evaluated their pain as 40 or more on a scale of 0 (no pain) to 99 (intolerable pain). Exclusion criteria were: coexisting illness or condition that might render administration of the naproxen sodium unusually hazardous or require medication that might interfere with the evaluation of the results; active peptic ulcers within 6 months of the trial; known bleeding problems or a requirement for anticoagulant therapy. Before surgery, demographic data and relevant medical histories were obtained from all candidates, and an appropriate physical examination was performed. All patients gave written consent, and the provisions of the Helsinki agreement were observed.

**Medication and Regimens**

Study medication consisted of naproxen sodium 275 mg capsules and matching placebo to preserve the double-blind design. Patients on the high-dosage regimen (1,650 mg/day for 2 days) took two capsules of active drug (a 550 mg dose) at 6 AM, 2 PM, and 10 PM each day. Those on the low-dosage regimen (1,100 mg day, 1,825 mg day 2) took two capsules of active drug at 6:00 AM on day 1, followed by one active and one placebo capsule at the same times as the group taking higher doses. No analgesic aside from the study drug was permitted during the trial; all concomitant medication was noted.

**Assessments**

At 6:00, 6:30, 7:00, 8:00, 9:00 and 10:00 AM, and at 12:00, 2:00, 4:00, 6:00, 8:00, and 10:00 PM on both study days (Fig. 1), patients evaluated the intensity of their pain on a scale from 0 (no pain) to 99 (intolerable pain). At the same time, they were asked whether they had experienced any unusual effects. The investigators then assessed the severity of the complaints and determined the cause, whether the study drug, concomitant medications, "other," or "unknown." Sleeping patients were awakened for evaluations; persons collecting the data were asked to pose all questions in the same words and manner to avoid introducing unintentional bias. At the end of the trial, patients evaluated overall efficacy of treatment on a scale of 1 to 5 (1 = excellent, to 5 = poor).

**Standard Calculations and Statistical Analyses**

Two indices were derived from the patient pain evaluation data. Pain intensity difference (PID) was calculated by subtracting the intensity of pain recorded at each interview from the intensity of pain at the start of the study (6:00 AM, day 1). Summed pain intensity difference (SPID) for a particular interview on day 1 was calculated by summing the PIDs from 4:00 PM, day 1 (the time of the first differential dosage) to the time of the interview; day 2 SPIDs included PIDs from 6:30 AM, day 2.

The large number of investigators and the disparate numbers of patients at each center precluded analysis of investigator/treatment interaction. Therefore, data were analyzed parametrically by the unequal variance t-test and nonparametrically by the Wilcoxon (Mann-Whitney) test and likelihood ratio chi-square test, all of which ignore investigator effects and investigator/drug interactions. All P-values are two-tailed; significance was defined as $P \leq .05$. All analyses were performed with SAS.$^{12}$

Because pain intensity scores recorded on day 1 from 6:30 AM to 2:00 PM were obtained before the dosage was different for the two treatment groups, these scores were not included in the efficacy analy-
sis. Also, patients were excluded from statistical analysis for efficacy if evaluations through at least 8:00 PM on day 1 were not recorded. To ensure a constant cohort of patients for evaluation throughout the study and to include as much patient data as possible, appropriate adjustments to the data were made. At no time were data adjusted in more than 20% of patients' scores, and the adjustments approached 20% only at the end of the study, because of terminations for inadequate relief of pain. Analysis of nonadjusted scores verified that the adjustments were conservative, erring, if at all, on the side of reducing the differences between the regimens.

**Results**

**Patient Population**

One hundred forty-seven patients were admitted to the study at eight centers. Males comprised 59% of patients, and the average age was 49.2 years (range, 19.4 to 83.7 years). Both sexes had strongly bimodal age distributions, with the first mode in the mid 20s, the antimode in the mid to late 40s, and the second mode in the late 60s. Approximately two-thirds of the women were in the older mode and two-thirds of the men were in the younger mode. There were no statistically significant differences between the two test groups in sex, race, age, or baseline pain scores (Table). Differences were found between investigators in measures of sex (P = .04) and race (P < .001), but the distribution between regimens remained unbiased.

**Withdrawals**

Of 143 patients treated with the study medication, 99 were eligible for the efficacy analysis (45 in the low-dosage group and 54 in the high-dosage group). Of those lost to efficacy analysis (25 in the low-dosage and 23 in the high-dosage group), 12 had insufficient pain at baseline to qualify, 15 had inadequate pain relief and withdrew before 8:00 PM, day 1, one had an adverse event (abdominal pain), three took prescribed medications, two broke the drug code, and 11 withdrew for other (or multiple) reasons, not including inadequate relief or complaints. Data of one patient who received heparin for anticoagulant therapy were included.

**Efficacy**

There were no statistically significant differences between the two regimens at any point in the trial. Patients began both regimens (6:00 AM, day 1) with nearly equal mean adjusted baseline pain scores: 62.9 for those taking high doses and 60 for those taking low doses (P = .31). By hour 8 (2:00 PM, day 1, the last interview before differential dosing began), mean pain intensity for patients in the group randomized to the low-dosage regimen had declined approximately 38% to 37, while mean pain intensity for the group randomized to the high-dosage regimen declined approximately 40% to 37.8. Because both groups had taken the same dosage up to hour 8, this similarity in the decrease in mean pain intensity was expected. By the last evaluation of day 1 (hour 16, 10:00 PM), the mean pain score for the
In a separate analysis, patients who had knee or ankle surgery were compared with those who had hip or shoulder operations, with respect to the performance of the two regimens. The group that had knee or ankle surgery responded similarly to both regimens. However, the group that had shoulder or hip surgery appeared to respond better to the high-dosage regimen. For this group, the difference between regimens for change in PIDs from hour 16 (10:00 PM, day 1) to hour 24 (6:00 AM, day 2) approached significance ($P = .07$). During day 2, the superior efficacy of the higher dosage in these patients continued to be evident (Fig. 3), although the differences were not statistically significant.

**Adverse Events**

Of 143 treated patients, 21 patients taking the low-dosage regimen and 23 taking higher doses reported adverse events. Of 124 patients who took at least the second dose of medication, 10 of 60 (17%) on low dosage reported 17 complaints; 14 of 64 (22%) using higher doses reported 23 complaints. Two of these patients receiving high-dose medication had one severe complaint each (abdominal pain and nausea), and one patient receiving lower doses had three severe complaints (nausea, shakes, nervousness); these complaints were judged by the investigators to be caused by the study drug. There was no significant difference between the two regimens in the number of patients reporting complaints ($P = .46$).

Gastrointestinal complaints predominated. Of nine patients who withdrew because of adverse events, three had taken only the initial 550 mg of naproxen sodium and two of these reported similar complaints even before that first dose. The remaining six withdrew after more than one dose of study medication; five had gastrointestinal complaints and one taking higher doses reported drowsiness. There was no statistically significant difference between the two regimens in the number of patients withdrawing from the trial because of adverse events, although five patients taking the high-dosage regimen and only one taking lower doses withdrew for this reason.

**Discussion**

A trend toward overall superiority of the higher dosage was evident in the more sustained pain relief provided by the high-dosage regimen between hours 10 and 16, and in PID and SPID scores throughout the second day, although the differences were not
statistically significant. This high-dosage advantage was more apparent when the results were analyzed by site of surgery. The difference in efficacy between the two regimens was negligible in the treatment of pain after knee or ankle surgery. However, it should be noted that patients who had knee or ankle surgery had a more rapid decrease in pain levels than those who had hip or shoulder surgery, suggesting that the former group may have had more difficulty in discriminating between two dosages of analgesic. Thus, by hour 8 of the first day (the last evaluation before dosage differentiation), 58% of patients with knee or ankle surgery had a pain intensity score of 20 or less, as compared with 38% of the other patients. Also, six of the patients with knee or ankle surgery withdrew from the study early with no pain, while none of the other patients did.

For the group that had hip or shoulder surgery, the difference between the regimens in overnight change of PID's approached significance in favor of the higher dosage. Throughout day 2, PID and SPID scores continued to show a trend toward overall superiority in efficacy for the group taking the high-dosage regimen, although the difference was not statistically significant. It appears that because pain after hip or shoulder surgery persists relatively longer, sufficient pain was present on the second day to allow demonstration of more sustained pain relief by higher doses of naproxen sodium. Thus, for patients who have had hip or shoulder surgery, a regimen of 550 mg thrice daily may be cumulatively more efficacious in the treatment of postoperative pain than a 550 mg initial dose followed by 275 mg three times a day.

There were no statistically significant differences between the regimens for adverse events. It is possible that some of the predominant gastrointestinal complaints were due to factors other than study medication, such as medication prior to the study or surgical anaesthesia.

References