Effectiveness and Tolerability of Once-Daily Nimesulide Versus Ibuprofen in Pain Management After Surgical Extraction of an Impacted Third Molar: A 24-Hour, Double-Blind, Randomized, Double-Dummy, Parallel-Group Study

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ABSTRACT

Background: Nimesulide is a nonsteroidal, anti-inflammatory drug that has been used for a wide range of acute and chronic pain. A once-daily formulation of nimesulide is now commercially available, but its effectiveness in pain management after dental surgery has not been assessed.

Objective: The aim of this study was to assess the analgesic effectiveness and tolerability of oral treatment with once-daily nimesulide versus ibuprofen q6h over 24 hours in patients with postoperative pain associated with surgical extraction of an impacted third molar.

Methods: This 24-hour, double-blind, randomized, double-dummy, parallel-group study was conducted at a private practice in Caracas, Venezuela. Patients aged between 12 and 60 years with moderate to severe pain after extraction of an impacted third molar were enrolled. Patients were randomized to receive a single dose of nimesulide (300-mg tablet) or ibuprofen (400-mg tablets) q6h for 24 hours. For double-dummy design, patients in the nimesulide group also received ibuprofen placebo tablets, to be taken q6h for 24 hours, and patients in the ibuprofen group received a nimesulide placebo tablet. The primary end points were pain intensity (PI) and pain relief scores over 24 hours. Secondary end points included total pain relief, PI difference (PID), sum of PID (SPID), time to first measurable change in PI (ie, PID ≥ 10 mm), and use of rescue medication (acetaminophen). Patients also rated the treatment's effectiveness as very poor to very good on questioning by the study investigator. Spontaneously reported adverse effects (AEs) were recorded.

Results: Eighty-six patients were enrolled (56 females, 30 males), with 43 patients per treatment group (mean age: nimesulide group, 25.2 years; ibuprofen group, 24.2 years). The baseline characteristics were statistically similar between the 2 groups. Compared with baseline, mean PI scores were significantly lower in both treatment groups at all time points throughout the study ($P < 0.001$). Mean

PI scores were significantly lower in the nimesulide group compared with the ibuprofen group at 15 and 45 minutes and 1 hour after study drug administration ($P \leq 0.049$). Time to first measurable change in PI was within the first 15 minutes in 22 patients (52%) in the nimesulide group and in 14 patients (33%) in the ibuprofen group ($P = 0.03$). Analgesia lasted 24 hours with nimesulide and ibuprofen (PI scores at 24 hours, 9.4 and 3.6, respectively). The mean PR score was significantly lower in the nimesulide group compared with the ibuprofen group at 1 hour after study drug administration ($P = 0.049$). Compared with baseline, PID and SPID were significantly higher in both treatment groups throughout the study ($P < 0.001$). Significantly more patients in the nimesulide group than in the ibuprofen group reported that treatment provided effective pain relief (82% vs 73%; $P = 0.013$). No AEs were reported in either treatment group throughout the study. Use of rescue medication was statistically similar between the nimesulide and ibuprofen groups (38% and 31%, respectively).

Conclusions: In this study of patients with moderate to severe pain after extraction of impacted third molars, nimesulide and ibuprofen provided effective 24-hour relief. However, the results suggest that the analgesic effect of nimesulide had a faster onset (<15 minutes) and was stronger (based on patient opinion) than that of ibuprofen. Both study drugs were well tolerated. (*Curr Ther Res Clin Exp.* 2005;66:172–180) Copyright © 2005 Excerpta Medica, Inc.

Key words: nimesulide, ibuprofen, dental pain, programmed liberation.

INTRODUCTION

The pain that follows the extraction of an impacted third molar is an acute, short-lasting (2 hours to 3 days) pain that reaches its maximum intensity during the early (first 4 hours) postextraction period. This type of pain is widely used to evaluate the effectiveness of analgesic agents, especially in single doses.^{1–4}

Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in relieving mild or moderate pain, and they are more likely to be used in ambulatory patients compared with their injectable counterparts. The analgesic action of nimesulide has been documented in a wide range of acute and chronic pain.^{1–4} Nimesulide is an NSAID with pharmacodynamic properties that differ from those of other compounds in the same class. In addition to inhibiting the pain receptors associated with the generation of prostaglandins, nimesulide inhibits the release of oxidizers from activated neutrophils. This drug also has a scavenger effect on hypochloric acid, which, combined with the proteolytic enzymes produced by these neutrophils during the inflammatory process, result in toxicity in tissues.^{5,6}

Nimesulide decreases histamine release by mastoid cells and inhibits the production of platelet-activating factor in basophils. The cyclooxygenase (COX)-1/COX-2 ratio of nimesulide results in excellent tolerability, including a low incidence (9%) of gastrointestinal adverse effects (AEs).⁷

An oral formulation (300-mg tablet) of controlled-release nimesulide* developed in 2003 allows for once-daily dosing. A 100-mg dose is released immediately after administration to allow pain relief within 1 hour, and a 200-mg dose is released over the subsequent 24 hours for a lasting analgesic effect. With the first dose, $T_{\max}$ is ≤ 4 hours. With repeated dosing, $T_{\max}$ is ≤ 2 hours, and a therapeutic concentration is maintained for 24 hours.

Ibuprofen, the first NSAID derived from propionic acid, is used for mild or moderate pain (eg, in dysmenorrhea) at dosages of 200 to 400 mg q4–6h. It is absorbed quickly after administration. $T_{\max}$ is 1 to 2 hours, and $t_{1/2}$ is ~2 hours. Ibuprofen is cleared rapidly and completely, with 90% of the dose being excreted in the urine as metabolites or their conjugates. However, in 5% to 15% of cases, ibuprofen is associated with gastrointestinal AEs, including epigastric pain, nausea, and fullness. To minimize the risk for these AEs, ibuprofen should be given with food. Thrombocytopenia, cutaneous eruptions, visual disturbance, fluid retention, and edema occur less frequently.⁴

The aim of the present study was to assess the onset of the analgesic effect and the effectiveness and tolerability of oral treatment with a single dose of nimesulide 300 mg versus ibuprofen 400 mg q6h over 24 hours in patients with moderate or severe pain after surgical extraction of an impacted third molar.

PATIENTS AND METHODS

This 24-hour, double-blind, randomized, double-dummy, parallel-group study was conducted at a private practice in Caracas, Venezuela. After surgery but before administration of the study drugs, patients were assigned, using a computer-generated table of random numbers, to 1 of 2 treatment groups: a single dose of nimesulide (300-mg tablet) or ibuprofen[†] (400-mg tablets) q6h for 24 hours. For double-dummy design, patients in the nimesulide group also received ibuprofen placebo tablets, to be taken q6h for 24 hours, and patients in the ibuprofen group received a nimesulide placebo tablet. The patients were evaluated over a 24-hour period at 5, 10, 15, 30, and 45 minutes and 1, 6, 12, and 24 hours after surgery.

A variety of measures were used to determine the effectiveness of the treatments. Pain intensity (PI) was rated on a 100-mm visual analog scale (VAS) (0 = no pain to 100 = worst pain imaginable), and pain relief (PR) was rated on a 5-point scale (0 = no relief; 1 = little relief; 2 = some relief; 3 = much relief; and 4 = complete relief). Total PR (TOPAR) was calculated as the sum of the PR scores at 15, 30, and 45 minutes and 1, 6, 12, and 24 hours ($\sum[PR \times h]_{1 \rightarrow n}$). The PI difference (PID) and the sum of the PIDs (SPID) ($\sum[PI_n - PI_{n-1}]_{1 \rightarrow n}$) were also calculated. Time to PID ≥ 10 mm was considered the first measurable change in PI (ie, the onset of analgesic effect). Use of rescue medication (acetaminophen 500-mg tablet or corticosteroids) was recorded. Patients also rated the effectiveness of the treatment in response to the following multiple-choice question

*Trademark: Normodual® (Biocontrolled Laboratories, Caracas, Venezuela).

†Trademark: Brugesic® (Laboratorios Elmor, Caracas, Venezuela).

posed by the investigator: "In your opinion, did the medication relieve your pain very poorly, poorly, moderately, well, or very well?"

Healthy female and male patients between 12 and 60 years of age who had undergone surgical extraction of impacted third molars, had moderate to severe postoperative pain (PI score, 40–80), and were able to understand the procedures they were to follow were eligible for the study.

All patients provided written informed consent to participate in this trial. Consent for patients aged <18 years was also provided by their legal representatives. The study protocol was approved by an independent ethics committee.

Extraction of a third molar was performed with patients under local or general anesthesia, using a standard technique. The operative time (from the first incision to the end of suturing) was recorded by the investigator for each patient.

Use of short-acting analgesics was prohibited for 6 hours before surgery, and use of long-acting analgesics was prohibited for 24 hours before surgery. Patients with a known sensitivity to NSAIDs, any cardiac condition, renal or hepatic dysfunction, history of or an existing gastrointestinal condition, drug dependency, alcohol abuse, hypertension, uncontrolled diabetes mellitus, or hematologic dysfunction or coagulopathy were excluded from the study. Pregnant or breast-feeding women were also excluded.

AEs reported spontaneously by patients during the 24-hour study period were recorded by the investigator.

Use of NSAIDs other than the study drugs was prohibited. Acetaminophen (500-mg tablet) was allowed as rescue medication. The patient could use acetaminophen as early as 30 minutes after study drug administration, provided that the acetaminophen use was carefully recorded. Corticosteroids were allowed for use as anti-inflammatory medication as early as 1 hour after study drug administration, provided that the intake time, dose, and route of administration were recorded by the investigator.

Statistical Analysis

Analysis of variance was carried out for age, body weight, height, systolic and diastolic blood pressure (SBP/DBP), and PI scores. PID, SPID, PR, and TOPAR were analyzed using the Wilcoxon range test (intragroup) and the Mann-Whitney *U* test (intergroup). The numbers of patients who used rescue medication and patients' opinions of the drugs' effectiveness were evaluated using the Fisher exact test at $\alpha = 0.05$ and $\beta = 0.1$. This study was calculated to have >95% power to detect differences in PI score of 10% between treatments, and a 5% α error. $P < 0.05$ was considered statistically significant. SPSS version 7.5 (SPSS Inc., Chicago, Illinois) was used for the statistical calculations.

RESULTS

The study included 86 patients (56 females, 30 males) divided into 2 groups of 43 patients each (mean age: nimesulide group, 25.2 years; ibuprofen group,

24.2 years). The baseline demographic and clinical characteristics were statistically similar between the 2 groups (**Table I**). The 2 groups were also statistically similar in terms of indications for surgery.

The most common diagnoses in both groups were inadequate jawbone space (nimesulide group, 25 patients [58%]; ibuprofen group, 22 patients [51%]), improper angulation of the tooth (11 [26%] and 13 [30%] patients, respectively), and the need for space for orthodontia (7 [16%] and 8 [19%] patients, respectively).

The pain began during the first 2 hours after the removal of the impacted third molar in 18 patients (42%) receiving ibuprofen and in 22 (51%) receiving nimesulide. Pain started 2 to 4 hours after extraction in 20 (47%) and 14 (33%) patients in the nimesulide and ibuprofen groups, respectively. Seven patients (16%) in the nimesulide group experienced pain <1 hour after the intervention compared with 3 patients (7%) in the ibuprofen group. None of these differences were statistically significant.

In both groups, the mean PI score was significantly lower at all time points compared with baseline (all, $P < 0.001$). At 15 and 45 minutes and 1 hour, the mean (SD) PI scores were significantly lower in the nimesulide group compared with the ibuprofen group (15 minutes: 37.3 [19.2] vs 44.6 [18.6]; $P = 0.047$; 45 minutes: 18.2 [20.0] vs 28.1 [22.6]; $P = 0.033$; and 1 hour: 13.1 [19.2] vs 20.8 [19.6]; $P = 0.049$); at all subsequent time points, the scores were statistically similar between the 2 groups (**Table II**).

The first significant change of ≥ 10 mm on the VAS (ie, onset of action) was observed in the first 15 minutes by 22 patients (51%) in the nimesulide group compared with 14 (33%) in the ibuprofen group ($P = 0.03$) (**Table III**).

Table I. Baseline demographic and clinical characteristics of the study patients (N = 86).

Characteristic	Nimesulide (n = 43)	Ibuprofen (n = 43)	P
Age, y			0.61
Mean	24.2	25.2	
Range	14–52	15–25	
Sex, no. (%)			1.0
Female	28 (65)	28 (65)	
Male	15 (35)	15 (35)	
Body weight, mean (SD), kg	64.6 (18.6)	63.4 (15.6)	0.75
Height, mean (SD), cm	1.7 (0.1)	1.7 (0.1)	0.73
Blood pressure, mean (SD), mm Hg			
Systolic	113.0 (7.5)	112.0 (7.4)	0.60
Diastolic	69.1 (8.7)	66.4 (8.0)	0.16

Table II. Mean (SD) pain intensity scores* after administration of single-dose nimesulide 300 mg or ibuprofen 400 mg q6h for 24 hours for postoperative analgesia in patients undergoing dental surgery (N = 86).[†]

Study Group	0 Min	15 Min	30 Min	45 Min	1 H	6 H	12 H	24 H
Nimesulide (n = 43)	48.4 (11.3)	37.3 (19.2)	26.4 (22.1)	18.2 (20.0)	13.1 (19.2)	8.2 (14.5)	5.4 (11.5)	9.4 (8.7)
Ibuprofen (n = 43)	50.2 (12.8)	44.6 (18.6) [‡]	35.4 (24.3)	28.1 (22.6) [§]	20.8 (19.6)	10.5 (15.4)	5.6 (10.8)	3.6 (8.8)

*As measured on a 100-mm visual analog scale: 0 = no pain to 100 = worst pain imaginable.

[†]P < 0.001 versus baseline (0 min) at all time points in both treatment groups.[‡]P = 0.047 versus nimesulide.[§]P = 0.033 versus nimesulide.^{||}P = 0.049 versus nimesulide.

Table III. Measures of pain intensity and changes in pain after administration of single-dose nimesulide 300 mg (n = 43) or ibuprofen 400 mg q6h for 24 hours (n = 43) for postoperative analgesia in patients undergoing dental surgery.*

Scale	15 Min	30 Min	45 Min	1 H	≥6 H	12 H	24 H
First significant change PID (≥10 mm)							
Nimesulide, no. (%)	22 (51)	10 (23)	4 (9)	4 (9)	3 (7)	–	–
Ibuprofen, no. (%)	14 (33)	15 (35)	6 (14)	4 (9)	4 (9)	–	–
<i>p</i> [†]	0.03	–	–	–	–	–	–
PID [‡]							
Nimesulide	11.1	22.7	30.2	35.3	40.2	43.1	39.0
Ibuprofen	8.0	16.5	23.4	29.4	40.0	44.9	47.0
<i>p</i> [§]	0.145	0.131	0.094	0.165	0.913	0.772	0.123
SPID							
Nimesulide	11.8	33.7	63.9	99.2	139.4	182.4	221.4
Ibuprofen	8.0	24.5	48.0	77.4	116.4	160.2	206.1
<i>p</i> [§]	0.093	0.107	0.064	0.066	0.058	0.084	0.233
PR score							
Nimesulide	1.2	1.9	2.6	3.0	3.5	3.6	3.5
Ibuprofen	0.9	1.7	2.4	2.5	3.2	3.5	3.6
<i>p</i> [§]	0.146	0.551	0.280	0.049	0.097	0.658	0.321
TOPAR							
Nimesulide	1.2	3.2	5.1	8.7	12.1	15.8	19.1
Ibuprofen	0.9	2.6	5.0	7.4	12.7	14.0	17.6
<i>p</i> [§]	0.146	0.294	0.308	0.160	0.965	0.067	0.136

PID = pain intensity difference; SPID = sum of PID; PR = pain relief; TOPAR = total PR.

* $P < 0.001$ versus baseline for all scores in both treatment groups.

†Wilcoxon range test.

‡As measured on a 100-mm visual analog scale: 0 = no pain to 100 = worst pain imaginable.

§Mann-Whitney *U* test.

||Scale: 0 = no relief; 1 = little relief; 2 = some relief; 3 = much relief; and 4 = complete relief.

Analgesia lasted 24 hours in both groups, as indicated by the mean PI scores (9.4 and 3.6 in the nimesulide and ibuprofen groups, respectively).

In both groups, the mean PID and the SPID values were significantly higher at all time points compared with baseline (all, $P < 0.001$); PID and SPID were statistically similar between the 2 groups at all time points (**Table III**).

In both groups, the mean PR and TOPAR scores were significantly higher at all time points compared with baseline (all, $P < 0.001$) (**Table III**). At 1 hour, the mean PR score was significantly higher in the nimesulide group compared with the ibuprofen group (3.0 vs 2.5; $P = 0.049$).

Rescue medication use was statistically similar between the nimesulide and ibuprofen groups (16 [38%] vs 13 [31%] patients, respectively). Most patients

needing rescue medication in the nimesulide group needed it between 2 and 4 hours after study drug administration; in the ibuprofen group, rescue medication was given most often between 4 and 6 hours after study drug administration. Twenty-seven (63%) and 31 (74%) patients received steroids in the nimesulide and ibuprofen groups, respectively.

Thirty-five (81%) and 31 (72%) patients receiving nimesulide and ibuprofen, respectively, indicated that the analgesic effect of the study drug was good or very good ($P = 0.013$).

None of the patients reported any AEs during the 24-hour duration of the study.

DISCUSSION

Several analgesic drugs have been shown to be effective in the treatment of pain after the surgical extraction of an impacted third molar. In the double-blind, clinical study by Walton et al⁸ (200 patients), the NSAIDs ketorolac 30 mg IV and diclofenac 75 mg IV, administered with patients under general anesthesia and 4 hours after the IV dose, were more effective, as measured on the VAS, compared with vehicle ($P = 0.002$) and provided a similar degree of pain relief in patients with this type of pain.

In a randomized, active-controlled, parallel-group study in 128 patients, Jung et al⁹ found that the combinations of tramadol-acetaminophen 75/650 mg and codeine-acetaminophen-ibuprofen 20/500/400 mg in single doses were comparable in the onset of analgesia and analgesic efficacy, as measured on the VAS, in acute postoperative dental pain.

In other studies, a single dose of valdecoxib 40 mg compared with a single dose of rofecoxib 50 mg administered postoperatively provided a similar magnitude of analgesic effect, as measured by line-weighted TOPAR at 6 hours after dosing.^{10,11}

In a randomized, double-blind study, Zelenkas et al⁴ compared the efficacy of single-dose lumiracoxib 100 to 400 mg, ibuprofen 400 mg, and placebo over 12 hours in 202 patients with postoperative dental pain. The primary efficacy end point was PID, which was significantly different in the 2 groups receiving active drugs compared with the placebo group from 1 to 12 hours after dosing.

In a single-dose, randomized, active-controlled, parallel-group trial in 130 patients undergoing surgical extraction of a third molar, Bracco et al¹² found that rofecoxib 50 mg/d and nimesulide 200 mg/d, given for 6 days after surgery, provided similar effects on clinical signs of local postoperative inflammation.

Ibuprofen and conventional nimesulide require administration several times a day. The once-daily nimesulide formulation used in the present study provided analgesia throughout the 24-hour study period. Furthermore, the onset of analgesic effect was faster (<15 minutes) with single-dose nimesulide compared with ibuprofen 400 mg q6h. The duration of pain relief (the entire 24-hour observation period) was similar with both drugs, as measured using PI and PR scores.

CONCLUSIONS

In this study of 86 patients undergoing surgical extraction of impacted third molars, single-dose nimesulide provided analgesia similar to ibuprofen q6h over 24 hours. The group receiving nimesulide had a faster analgesic effect (<15 minutes) and a better patient rating of effectiveness compared with those receiving ibuprofen.

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