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Authors

Levick, S
Jacobs, C
Loukas, D F
[et al.](#)

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Naproxen sodium in treatment of bone pain due to metastatic cancer

Stanley Levick ^a, Charlotte Jacobs ^b, Demetrius F. Loukas ^c, David H. Gordon ^d,
Frank L. Meyskens ^e and K. Uhm ^f

^a Division of Hematology and Oncology, Albert Einstein Medical Center, Northern Division, Philadelphia, PA 19141 (U.S.A.),

^b Division of Oncology, Stanford University School of Medicine, Stanford, CA 94305-5306 (U.S.A.),

^c Central Texas Oncology Association, Austin, TX 78705 (U.S.A.), ^d University of Texas Health Science Center,

San Antonio Tumor and Blood Clinic, San Antonio, TX 78217 (U.S.A.), ^e University of Arizona Health Sciences Center, Arizona Cancer Center, Tucson, AZ 85724 (U.S.A.), and ^f Department of Oncology, Tri-Hospital Hospice, Passaic, NJ 07055 (U.S.A.)

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Summary This multicenter, double-blind, randomized, parallel study compared the efficacy and safety of two dosages of naproxen sodium (NS) in 100 patients with bone pain due to metastatic cancer. Patients were asked to rate their pain on a scale of 0-99; those patients with pain scores of 40 or more (indicating moderate to severe pain) were enrolled. Patients receiving the high-dosage regimen (HDR; n = 51) received NS 550 mg every 8 h for 3 days. Those receiving the low-dosage regimen (LDR; n = 49) received on day 1 an initial dose of NS 550 mg followed by NS 275 mg capsules every 8 h through day 3. Patients evaluated pain intensity 8 times/day. During use of NS, pain intensity scores decreased by approximately one-third in each treatment group. Among patients who responded to NS, pain relief with the HDR was significantly greater than with the LDR. Differences between regimens in adverse events during treatment were non-significant; complaints were mainly gastrointestinal and mild.

Key words: Naproxen sodium; Non-steroidal anti-inflammatory drugs; Pain; Bone metastases

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs for the relief of mild to moderate pain. Some investigators have found that the NSAID naproxen sodium is also effective in relieving moderate to severe musculoskeletal, postoperative, post-partum, and dysmenorrheic pain [1,4,5,10,11]. In double-blind studies, when compared to

acetaminophen or oral pentazocine, naproxen sodium provided greater relief in patients with moderate to severe postoperative pain [4,8].

Naproxen sodium, like other members of the NSAID class of drugs, produces analgesia primarily by inhibiting the synthesis of prostaglandins. In cancer patients, the pain associated with bony metastases appears to be mediated by prostaglandins [7,9,12], with both PGE₁ and PGE₂ producing hyperalgesia through nociceptor sensitization [3]. The analgesic efficacy of naproxen sodium, coupled with its good tolerability, warranted investigation of this prostaglandin inhibitor as a non-narcotic alternative for cancer patients who suffer from severe, debilitating pain due to tumor metastases to the bone.

Correspondence to: Stanley Levick, M.D., Division of Hematology and Oncology, Albert Einstein Medical Center, Northern Division, Philadelphia, PA 19141, U.S.A.

The purpose of this study was to compare the efficacy and tolerability of naproxen sodium administered in a high-dosage regimen (HDR, 1650 mg/day on days 1–3) to a lower-dosage regimen (LDR, 1100 mg on day 1 followed by 825 mg on days 2 and 3) in patients with bone pain due to metastatic cancer.

Methods

Patients

A total of 145 inpatients and outpatients was enrolled by 17 investigators in this multicenter, randomized, double-blind, parallel trial. Patients who entered the trial had persistent bone pain due to metastatic cancer and were willing to forego analgesics for 6 h prior to the study as confirmed in their written informed consent. Each patient included in efficacy analyses recorded a baseline pain intensity of at least 40 on a scale of 0 (no pain) to 99 (intolerable pain). Prior to starting the study, the status of the primary tumor and metastases and the type of cancer therapy were recorded for each patient. Pregnant or lactating women, patients with other medical conditions with pain as a prominent symptom, those taking anti-inflammatory medications, or those receiving other forms of treatment, including chemotherapy or radiation, that could affect pain assessment were excluded from the trial. Also excluded were patients with significant co-existing illness including gastrointestinal, hepatic, renal, or other diseases that might have rendered administration of the study medication unusually hazardous. Patients with a history of hypersensitivity to aspirin, codeine, naproxen sodium, or any other non-steroidal anti-inflammatory drug, a history of bleeding problems or of active peptic ulcers within 6 months preceding the trial, anticoagulant therapy within the preceding 4 weeks, known alcohol or drug abuse, or dependence on opiate derivatives, synthetics, or combinations were also excluded. Those patients meeting the admission criteria were randomly assigned to either the high-dosage or low-dosage regimen. Patients who were receiving other forms of pain management (e.g., electroanalgesia, acupuncture, alcohol, etc.)

continued such therapy unchanged throughout the course of the study. Patients were allowed to withdraw from the study at any time, for any reason.

Medication

Each dose consisted of 2 capsules: either 2 naproxen sodium (NS) 275 mg capsules or 1 NS 275 mg capsule and 1 matching placebo capsule. Both high- and low-dosage groups received on day 1 an initial loading dose of NS 550 mg. After the loading dose and through day 3, high-dosage patients received NS 550 mg every 8 h; low-dosage patients received NS 275 mg and placebo at 8 h intervals. For ethical reasons no placebo control group was included in this study.

Efficacy and safety assessment

Patients and investigators evaluated patients' pain intensity each day; a score of 40 or more indicated moderate to severe pain. Pain intensity was assessed at 06.00, 08.00, 10.00, 12.00, 14.00, 16.00, 18.00 and 20.00 h. When administration and evaluation times coincided, patients recorded their pain intensity scores just before taking their medication. Outpatients evaluated and recorded pain severity themselves and kept a complete daily record of concomitant medications. Attending health professionals recorded inpatients' pain severity evaluations and concomitant daily medications. On trial completion or termination, patients and physicians each gave an overall evaluation of medication effectiveness using a 4-point scale ('excellent,' 'good,' 'fair,' and 'poor'). Efficacy was further assessed by 2 calculated indices: pain intensity differences (PIDs; baseline pain intensity minus pain intensity at each evaluation time) and summed pain intensity differences (SPIDs; the sum of PIDs for each day). Pain intensity measures were analyzed parametrically (unequal variance *t* test) and non-parametrically (Wilcoxon/Mann–Whitney tests).

Patients were questioned about any unusual symptoms they may have experienced during the trial and physicians judged whether the symptoms were related to study medications. One hundred forty-three patients took medication and were included in the complaints analyses. The difference

between regimens in the number of patients reporting complaints was analyzed by the chi-square and Wilcoxon/Mann-Whitney tests.

Results

Of the 143 patients who took trial medication, 100 (51 high-dosage patients and 49 low-dosage patients) adhered to the study protocol and provided sufficient data to be considered valid for efficacy analyses; their average age was 62.3 years with a range from 18.9 to 80.5 years. There were no significant differences between the 2 study groups with regard to sex, race, age, or baseline pain scores. A demographic summary of the patients is presented in Table I.

Pain relief

Eighty-three patients who had pain relief during the 6 h following the initial NS 550 mg dose were considered NS responders. Seventeen other patients, considered non-responders, reported either worsening or no change in pain intensity during

the 6 h after the initial dose. (All patients in this study received high-dosage treatment at outset. In addition, all had cancer pain assumed to be relatively stable persistent pain. These two circumstances allowed categorization of patients as NS responders or NS non-responders.)

Analyses of the NS responder data showed statistically significant differences between regimens for most PIDs and SPIDs on day 3. A summary of responder PIDs and SPIDs is presented in Table II. Mean adjusted SPIDs are displayed in Fig. 1.

During treatment, a mean decrease in pain intensity of approximately one-third was seen in both regimen groups (see Fig. 2). In the high-dosage group, pain scores were consistently lower, and both PIDs and SPIDs were higher than those in the low-dosage group; however, when all valid patients (responders and non-responders) were evaluated, the differences between groups were not statistically significant.

Overall evaluations of effectiveness by NS responders and by physicians were not significantly different between dosage regimens ($P = 0.070$ and

TABLE I
SUMMARY OF PATIENT DEMOGRAPHICS

	Number of patients	Sex		Race *		Mean age (range)	Mean baseline pain score
		M	F	W	NW		
All patients	100	49	51	83	17	62.3 (19–81)	58.8 (40–99)
Low-dosage	49	23	26	39	10	59.9 (19–79)	58.2 (40–99)
High-dosage	51	26	25	44	7	64.5 (22–81)	59.4 (40–90)
Responder subset							
Low-dosage **	44	21	23	35	9	59.3 (19–79)	59.4 (40–99)
High-dosage	39	20	19	33	6	64.2 (22–81)	63.1 (40–90)
Non-responder subset							
Low-dosage	5	1	4	4	1	64.9 (46–73)	59.0 (40–85)
High-dosage	12	6	6	11	1	65.6 (53–78)	54.2 (40–90)

* W = white, NW = non-white.

** The higher percentage of responders in the low-dosage group as opposed to the high-dosage group is attributable to chance and is not statistically significant ($P = 0.072$).

TABLE II

MEAN PIDs * AND SPIDs ** FOR PATIENTS WHO RESPONDED TO NAPROXEN SODIUM

Hour after base	PIDs				SPIDs			
	Regimen ***		P values §		Regimen ***		P values §	
	Low	High	W/MW	t test	Low	High	W/MW	t test
10	20.8	30.4	0.09	0.11	20.8	30.4	0.09	0.11
12	21.7	31.4	0.09	0.11	42.4	61.8	0.09	0.10
14	19.4	27.0	0.29	0.22	61.8	88.8	0.09	0.13
16	17.8	27.7	0.12	0.12	79.5	116.5	0.10	0.12
24	16.0	24.9	0.12	0.18				
26	21.1	28.8	0.26	0.24	21.1	28.8	0.26	0.24
28	21.8	30.7	0.16	0.16	42.9	59.5	0.17	0.20
30	22.6	30.3	0.25	0.25	65.5	89.8	0.20	0.21
32	18.8	28.9	0.13	0.10	84.3	118.7	0.19	0.17
34	19.9	32.3	0.08	0.05	104.2	151.0	0.14	0.13
36	19.5	32.0	0.08	0.04	123.7	183.0	0.12	0.11
38	19.2	30.7	0.13	0.07	142.9	213.8	0.11	0.10
40	17.0	28.2	0.16	0.08	159.9	241.9	0.13	0.09
48	16.9	30.5	0.03	0.03				
50	19.6	30.0	0.12	0.09	19.6	30.0	0.12	0.09
52	18.3	31.1	0.04	0.03	37.9	61.1	0.07	0.05
54	17.9	31.4	0.05	0.03	55.8	92.5	0.05	0.04
56	17.6	30.2	0.07	0.05	73.4	122.7	0.05	0.04
58	16.7	32.6	0.02	0.01	90.2	155.3	0.04	0.03
60	17.2	31.3	0.05	0.03	107.4	186.6	0.05	0.03
62	16.2	30.4	0.05	0.03	123.6	217.0	0.04	0.03
64	17.0	29.4	0.09	0.06	140.6	246.4	0.05	0.03

* PIDs = pain intensity differences (baseline pain intensity minus pain intensity at each evaluation).

** SPIDs = summed PIDs.

*** Low-dosage, n = 44; high-dosage, n = 39.

§ Wilcoxon/Mann-Whitney and unequal variance t test P values.

$P = 0.092$, respectively), although a trend favoring the high-dosage regimen was apparent. These evaluations are summarized in Table III.

Among NS responders who terminated the trial because of inadequate pain relief, fewer ($P = 0.026$) high-dosage patients (4 out of 39) terminated than did low-dosage patients (13 out of 44). Of all valid patients (responders and non-responders), more ($P = 0.067$) low-dosage patients (14 out of 49) than high-dosage patients (7 out of 51) withdrew due to inadequate pain relief.

Tolerability

Because all patients received an initial NS 550 mg dose, comparison of high-dosage and low-dosage patients' complaints was meaningful only

for patients who took at least a second dose of medication ($n = 139$). Patient complaints were primarily gastrointestinal and were mild; a chi-square test revealed no significant difference between the two regimens in the numbers of patients reporting complaints. Twelve low-dosage patients (17%) and 15 high-dosage patients (22%) reported complaints; of these, 5 low-dosage (7%) and 11 high-dosage (16%) patients complained of gastrointestinal problems such as nausea, indigestion, and gastrointestinal upset. A total of 7 patients terminated the trial prematurely due to adverse events. Gastrointestinal problems caused 2 of the 7 patients to withdraw after the initial 550 mg dose; 3 high-dosage patients later withdrew for the same reason. Two low-dosage patients

Fig. 1. Mean adjusted SPIDs on days 1 through 3 for patients who responded to naproxen sodium.

Fig. 2. Mean pain intensity scores for all valid patients in naproxen sodium high-dosage and low-dosage groups.

TABLE III

RESPONDERS' AND PHYSICIANS' OVERALL EVALUATIONS OF EFFECTIVENESS

Response	Patient		Investigator	
	Low-dosage	High-dosage	Low-dosage *	High-dosage
Excellent	9	13	6	10
Good	9	11	11	12
Fair	8	5	12	9
Poor	18	10	14	8

* One investigator with one low-dosage patient did not evaluate effectiveness.

terminated because of 'other' problems (described as rash and dizziness, shaking and weak knees).

Discussion

In this study, naproxen sodium appeared to be effective in relieving bone pain due to metastatic cancer. Furthermore, in patients who responded to naproxen sodium treatment, a regimen of 550 mg TID was more effective than a dose of 550 mg followed by maintained use of 275 mg TID. Consistent with this, twice as many low-dosage as high-dosage patients dropped out because of inefficacy.

While effective pain relief is a crucial factor in improving the quality of life for cancer patients, there are, as with any drug regimen, risks involved when one opts to prescribe NSAID therapy to this population. For example, it is well known that gastrointestinal bleeding is one of the reported adverse effects associated with the class of NSAIDs; in cancer patients with coagulopathies such as disease- or chemotherapy-related thrombocytopenia, the possibility of an NSAID-related increase in gastrointestinal bleeding must be considered [6]. An additional concern involves the antipyretic properties of NSAIDs; it is possible that administration of these drugs could mask fever in immunocompromised cancer patients. Of interest in this regard are the findings of Chang [2], which suggest that this is unlikely with naproxen when fever is infectious rather than related to the neoplasm.

Conclusion

Either a 550 mg TID or a 275 mg TID naproxen sodium regimen provided pain relief in approximately 80% of the patients, after an initial 550 mg dose. Overall trends suggested that subsequent treatment on the high-dosage regimen was more effective than the low-dosage regimen in reducing the pain of bone metastases. In this study, the two regimens were equally well tolerated.

References

- 1 Brown, C.R., Sevelius, H. and Wild, V., A comparison of single doses of naproxen sodium, morphine sulfate, and placebo in patients with postoperative pain, *Curr. Ther. Res.*, 35 (1984) 511–518.
- 2 Chang, J.C., How to differentiate neoplastic fever from infectious fever in patients with cancer: usefulness of the naproxen test, *Heart Lung*, 16 (1987) 122–127.
- 3 Ferreira, S.H., Nakamura, M. and De Abreu Castro, M.S., The hyperalgesic effects of prostacyclin and prostaglandin E_2 , *Prostaglandins*, 16 (1978) 31–37.
- 4 Filtzer, H.S., A double-blind randomized comparison of naproxen sodium, acetaminophen and pentazocine in postoperative pain, *Curr. Ther. Res.*, 27 (1980) 293–300.
- 5 Hanson, F.W., Izu, A. and Henzl, M.R., Naproxen sodium in dysmenorrhea, *Obstet. Gynecol.*, 52 (1978) 583–587.
- 6 Kantor, T.G., Nonsteroidal anti-inflammatory analgesic agents in management of cancer pain. In: *Management of Cancer Pain. A Symposium*, Summer 1984, H.P. Publishing on behalf of Roche Laboratories, 1984, pp. 30–34.
- 7 Levy, M.H., Pain management in advanced cancer, *Semin. Oncol.*, 12 (1985) 394–410.
- 8 Ogilvie-Harris, D.J., Bauer, M. and Corey, P., Prostaglandin inhibition and the rate of recovery after arthroscopic meniscectomy. A randomized double-blind prospective study, *J. Bone Jt Surg.*, 67B (1985) 567–571.
- 9 Pollen, J.J. and Schmidt, J.D., Bone pain in metastatic cancer of prostate, *Urology*, 13 (1979) 129–134.
- 10 Ruedy, J. and McCullough, W., A comparison of the analgesic efficacy of naproxen and propoxyphene in patients with pain after orthopedic surgery, *Scand. J. Rheumatol., Suppl.* 2 (1973) 56–59.
- 11 Sevelius, H., Runkel, R., Segre, E. and Bloomfield, S.S., Bioavailability of naproxen sodium and its relationship to clinical analgesic effects, *Br. J. Clin. Pharmacol.*, 10 (1980) 259–263.
- 12 Twycross, R.G. and Lack, S.A., *Symptom Control in Far Advanced Cancer: Pain Relief*, Pitman Publ., London, 1983, pp. 119–123.