Utility of Naproxen in the Differential Diagnosis of Fever of Undetermined Origin in Patients with Cancer

JAE C. CHANG, M.D.
HOWARD M. GROSS, M.D.
Dayton, Ohio

The clinical utility of naproxen as an antipyretic agent was examined in the differential diagnosis of fever of undetermined origin in patients with cancer. Twenty-two patients with cancer and fever of undetermined origin for more than seven days were treated with naproxen to control fever when there was no evidence of infection after a careful initial evaluation, and in most cases, after failure of antibiotic therapy. In final analysis, none of five patients with infectious fever had responses to naproxen. In contrast, 14 of 15 patients with neoplastic fever showed a prompt, complete, and sustained lysis of fever within 24 hours after the initiation of naproxen treatment, and the patients also showed symptomatic improvement. One patient with neoplastic fever who did not have a response to naproxen had lysis of fever after the removal of necrotic tumor tissue. Two patients with fever from connective tissue disease had a partial lysis of fever in response to naproxen. These data suggest that naproxen specifically produces the lysis of neoplastic fever and, therefore, is a useful agent in assisting in the differential diagnosis of infectious fever and neoplastic fever in patients with cancer and fever of undetermined origin.

The evaluation and management of unexplained fever in patients with cancer, especially during intensive chemotherapy, is a very common and troublesome problem in clinical oncology practice. When persistent fever develops in patients and no obvious evidence of infection is present despite a careful physical examination and laboratory evaluation, the differential diagnosis of the fever becomes a true challenge to clinicians due to its urgency and necessity for appropriate treatment. Because host defenses in immunocompromised subjects can be altered by the underlying malignancy and/or its treatment, the possibility of the existence of life-threatening infection is very high; these patients are often treated with empiric measures, including various combinations of antibiotics, without a good foundation of infection. However, it is well known that fever that occurs by cancer itself without any infection is not an uncommon problem in patients with cancer [1–4].

Naproxen, a nonsteroidal anti-inflammatory agent that has proved usefulness in the treatment of a variety of arthritic conditions such as rheumatoid arthritis and osteoarthritis, has been shown to be as effective as aspirin in onset of action and reduction of fever [5]. In our institution, the drug has been used extensively in the treatment of fever in patients with cancer and suspected malignancy. Evaluation of clinical data and response of fever indicate that naproxen has its

From the Department of Medicine, Wright State University School of Medicine, and the Department of Internal Medicine, Good Samaritan Hospital and Health Center, Dayton, Ohio. This work was supported in part by the Oncology Research Grant of the Good Samaritan Foundation, Dayton, Ohio. Requests for reprints should be addressed to Dr. Jae C. Chang, Good Samaritan Hospital and Health Center, Dayton, Ohio 45406. Manuscript accepted September 20, 1983.

clinical value in the differential diagnosis of fever of undetermined origin. When fever is caused by bacterial infection, treatment with naproxen has had very little effect on the febrile course. On the other hand, naproxen treatment has usually resulted in a prompt and complete lysis of fever when it is caused by cancer itself. Clinical data were evaluated for the usefulness of naproxen in the differential diagnosis of fever of undetermined origin in patients with cancer.

PATIENTS AND METHODS

Twenty-two patients with fever of undetermined origin treated with naproxen at the Oncology Unit of the Good Samaritan Hospital and Health Center were selected for this evaluation and analysis. All patients had either cancer or suspected malignancy. The criteria for fever of undetermined origin were: (1) temperature at least once over 101°F, (2) duration of fever over one week, (3) no evidence of infection on careful physical examination, (4) negative results of adequate blood and urine cultures, (5) absence of pneumonia on chest roentgenography, (6) normal findings in spinal fluid in patients who underwent spinal puncture, (7) lack of evidence of drug fever. Only one patient had a documented fever less than seven days prior to the initiation of treatment with naproxen. In all patients, the temperature was recorded at least three times per day. Among 22 patients, 15 were initially treated with adequate courses of antibiotics and none had any significant response to treatment. Therefore, treatment with naproxen was initiated in these patients. Seven patients initially received naproxen alone because they were strongly suspected to have neoplastic fever. Since some of the patients were treated with intensive chemotherapy and had considerable bone marrow suppression, hematologic features were carefully recorded. Even during treatment with either antibiotics or naproxen, the possible cause of fever of undetermined origin was continuously sought with careful physical examination and laboratory studies. Final diagnoses of fever of undetermined origin in all patients were correlated with their response to antibiotics and naproxen.

The naproxen dosage was 250 mg twice a day at 12-hourly intervals when patients had persistent fever over 101°F. Duration of treatment was generally recommended to be not more than three days unless patients showed complete lysis of fever. If the response of fever was prompt and complete, treatment was continued at least seven days until patients showed definite clinical improvement and sustained normal temperature.

Adequate treatment was defined as a course of therapy with naproxen for at least three days. Therapeutic responses were defined as follows: complete response—complete lysis of fever to less than 99°F within 24 hours after the initiation of naproxen and sustained normal temperature for more than five days while receiving the drug; partial response—reduction of fever following naproxen, at least 2°F or more but higher than 99.4°F while receiving the drug. The symptomatic response was carefully observed in all patients and the lysis of fever was correlated with symptomatic improvement as well as with changes in the state of general well-being.

RESULTS

Patient Characteristics. **Table I** shows the clinical characteristics of 22 patients analyzed. There were 11 male and 11 female patients. The patients' ages ranged between 28 and 73 years old. The diagnosis of cancer was well established by an appropriate pathologic or hematologic examination in 20 patients. Four patients had acute leukemia and were receiving intensive induction chemotherapy. Four patients had colon cancer, three had chronic lymphocytic leukemia in stage III or IV, two had lung cancer, two had ovarian cancer, and one each had primary hepatocellular carcinoma, non-Hodgkin's lymphoma, chronic granulocytic leukemia, melanoma, and metastatic cancer to the bone marrow. Two patients were suspected to have cancer on admission but were proved not to have it during hospitalization. The known duration of fever was as long as 26 weeks, except for a patient with chronic granulocytic leukemia who had a documented fever for only four days. Chest roentgenography did not show enough evidence of an acute and active infectious process to account for fever. All patients had fever above 100°F, usually at least once per day, and it was as high as 104°F in four patients. Granulocyte counts were adquate in all patients except for four with acute leukemia who had severe granulocytopenia due to intensive induction chemotherapy. Anemia was present in all patients and the median hemoglobin level was 9.5 g/dl.

Treatment. As seen in **Table II,** 15 of 22 patients were initially treated with antibiotics, usually consisting of several drugs; none of these patients had any response to this therapy, which suggested a noninfectious process. Because of failure of antibiotic therapy, all 15 patients were then treated with naproxen. Nine patients had complete responses with the lysis of fever, two had partial responses, and four had no response. Further clinical follow-up and evaluation revealed that all nine patients with responses had fever from cancer (neoplastic fever). Of two patients with partial responses, one was found to have mixed connective tissue disease, the other systemic lupus erythematosus. Of the four patients with no response, two were found to have perirectal abscess, one had an infected Hickman's catheter, and one had ovarian cancer with massive tumor necrosis. In the last patient, the lysis of fever occurred only after the removal of necrotic tumor mass.

Seven of 22 patients were strongly suspected to have neoplastic fever after clinical evaluation and were treated with naproxen first. Five patients had complete lysis of fever in repsonse to the drug. However, naproxen treatment failed in two patients. Further evaluation

TABLE I Patient Data

Patient Number	Age/Sex	Diagnosis	Fever Duration (weeks)	Chest Roentgenographic Findings	Highest Temperature (°F)	Hematologic Data	
						White Blood Cells (mm^3)	Neutrophils (%)
1	59/F	Acute myeloblastic leukemia	2	Negative	104.0	1,800	0
2	53/F	Colon cancer	1	Negative	103.6	5,500	45
3	57/M	Chronic lymphocytic leukemia, stage IV	2½	Negative	103.8	4,900	15
4	46/M	Lung cancer	2	Cavitary lesion	101.6	4,000	90
5	61/M	Colon cancer	3	Infiltrate	102.6	9,900	72
6	54/M	Metastatic cancer	1	Negative	104.0	10,100	59
7	31/M	Hepatoma	1	Negative	103.0	10,000	73
8	65/F	Ovarian cancer	4	Pleural effusion	102.8	17,700	82
9	73/F	Non-Hodgkin's lymphoma, stage IV	1	Negative	102.4	3,400	81
10	28/F	Chronic granulocytic leukemia	½	Infiltrate	104.0	404,800	94
11	69/M	Chronic lymphocytic leukemia, stage III	1	Negative	101.0	8,500	14
12	65/M	Lung cancer	1	Lung mass	103.8	2,000	60
13	52/M	Colon cancer	9	Metastatic nodules	104.0	9,100	77
14	34/M	Melanoma	2	Metastatic nodules	102.5	11,200	82
15	64/F	Acute myelomonocytic leukemia	2	Negative	103.8	600	0
16	49/F	Acute myeloblastic leukemia	2	Negative	101.0	900	0
17	55/F	Chronic lymphocytic leukemia, stage IV	3	Lung mass	101.6	11,500	30
18	44/M	Colon cancer	1	Atelectasis	102.2	7,900	79
19	57/M	Acute myeloblastic leukemia	1	Negative	103.0	200	0
20	55/F	Ovarian cancer	6	Pleuritis	103.6	12,500	68
21	51/F	Mixed connective tissue disease	4	Pneumonitis	103.0	13,300	84
22	69/F	Systemic lupus erythematosus	26	Pleuritis	103.0	3,400	77

TABLE II Treatment Data

Patient Number	Antibiotics	Lysis of Fever with Antibiotics	Lysis of Fever with Naproxen	Cause of Fever
1	Ticarcillin, tobramycin	No	No	Infectious
2	Clindamycin, amikacin	Yes*	No	Infectious
3	Cefamandole, gentamicin, trimethoprim	No	No	Infectious
4	Isoniazid, rifampin	Yes*	No	Infectious
5	Vancomycin, moxalactam	No	No	Infectious
6	Cephalothin	No	Yes	Neoplastic
7	NT	(−)	Yes	Neoplastic
8	Cefoxitin, ampicillin, erythromycin	No	Yes	Neoplastic
9	Cefamandole, tobramycin, moxalactam	No	Yes	Neoplastic
10	NT	(−)	Yes	Neoplastic
11	NT	(−)	Yes	Neoplastic
12	Penicillin, gentamicin, erythromycin	No	Yes	Neoplastic
13	Cefamandole, gentamicin, erythromycin, clindamycin	No	Yes	Neoplastic
14	NT	(−)	Yes	Neoplastic
15	Ticarcillin, tobramycin	No	Yes	Neoplastic
16	Ticarcillin, tobramycin, ketoconazole	No	Yes	Neoplastic
17	Trimethoprim	No	Yes	Neoplastic
18	NT	(−)	Yes	Neoplastic
19	Ticarcillin, vancomycin	No	Yes	Neoplastic
20	Penicillin, cefamandole	No	No	Neoplastic
21	Nafcillin, gentamicin	No	Partial	Mixed connective tissue disease
22	Tetracycline	No	Partial	Systemic lupus erythematosus

* Had a response to antibiotics after naproxen failure.
NT = drugs not tried; (−) = not observed.

showed one patient had an intra-abdominal abscess and the other had possible tuberculosis. Both patients had responses to appropriate antibiotics.

Data on five patients with infectious fever are summarized in **Table III.** None of these patients had responses to naproxen but two had responses to antibiotics. The other two patients with perirectal abscess showed complete lysis of fever after incision and drainage.

Patterns of Response Fever to Naproxen. Neoplastic fever: Lysis of neoplastic fever was quite impressive. Not only did naproxen produce lysis of fever in 14 of 15 patients, but it also occurred promptly and completely within 24 hours after initiation of the drug. In addition, fever did not recur while patients were receiving naproxen (250 mg twice a day), and clinical and symptomatic improvement coincided with lysis of fever. Many patients, however, experienced excessive sweating during the initial lysis of fever but soon showed clinical improvement. **Figure 1** shows the failure of antibiotic treatment of neoplastic fever and the prompt response to naproxen in Patient 13. Therapy with antibiotics including cefamandole, gentamicin, and clindamycin failed in this patient. However, lysis of fever was prompt and sustained during naproxen therapy.

Fever of connective tissue disease: Two patients, one with mixed connective tissue disease and the other with systemic lupus erythematosus, had no evidence of infection on careful clinical evaluation. Both patients showed a partial and temporary lysis of fever with naproxen.

Infectious fever: In general, infectious fever resulted in very little modification with naproxen. When fever failed to abate in patients while they were receiving antibiotics and naproxen, the possibility of a hidden infection was considered; in all patients, the cause was found following further clinical and laboratory examination.

COMMENTS

Although naproxen has been widely used in clinical medicine as both an analgesic and anti-inflammatory agent [6–8], it has not been generally recognized as an antipyretic. Nevertheless, the drug has been demonstrated to have antipyretic activity [5,9]. The antipyretic effect of oral naproxen was comparable to that

TABLE III Patients with Infection (n = 5)

Patient Number	Diagnosis	Final Diagnosis of Cause of Fever	Response to Antibiotics	Response to Naproxen	Remarks
1	Acute myeloblastic leukemia	Perirectal abscess	No	No	Lysis after incision and drainage
2*	Colon cancer	Intra-abdominal abscess	Yes	No	Response to antibiotics
3	Chronic lymphocytic leukemia, stage IV	Perirectal abscess	No	No	Lysis after incision and drainage
4*	Lung cancer	Possible tuberculosis	Yes	No	Response to antituberculosis agents
5	Colon cancer	Infected Hickman's catheter	No	No	

* Treated with naproxen first prior to antibiotics.

of aspirin in a double-blind study of 102 children with fever [5] and, in other studies, was greater than that of phenylbutazone and aspirin and similar to that of indomethacin [9,10].

When naproxen was used in our institution as an antipyretic agent, especially in patients with an underlying malignancy, it became apparent that there were two different responses to the drug. Some patients had dramatic responses with prompt, complete, and sustained lysis of fever, and others had no lysis of fever in spite of several days of treatment. Careful clinical evaluation revealed that patients with neoplastic fever had responses to naproxen and those with infectious fever did not have responses to the drug.

Our follow-up studies have confirmed that naproxen is a useful agent in differentiating neoplastic fever from infectious fever, since lysis of fever occurred in all patients with neoplastic fever except for one with massive tumor necrosis. In this patient, however, immediate lysis of fever occurred after the removal of necrotic tumor mass. According to our data on a patient with cancer and fever of undetermined origin, the failure of fever to abate with naproxen therapy strongly supports the possibility of a bacterial infectious process. Occult infections such as abscess, meningitis, and encephalitis, and opportunistic infections as well as nonbacterial infections, should be considered in the differential diagnosis.

Fever of undetermined origin in patients with cancer, especially during intensive chemotherapy, poses a potential danger because of high morbidity and mortality unless the correct cause is established and appropriate treatment is instituted early. Since most episodes of fever in these patients are related to infection, bacte-

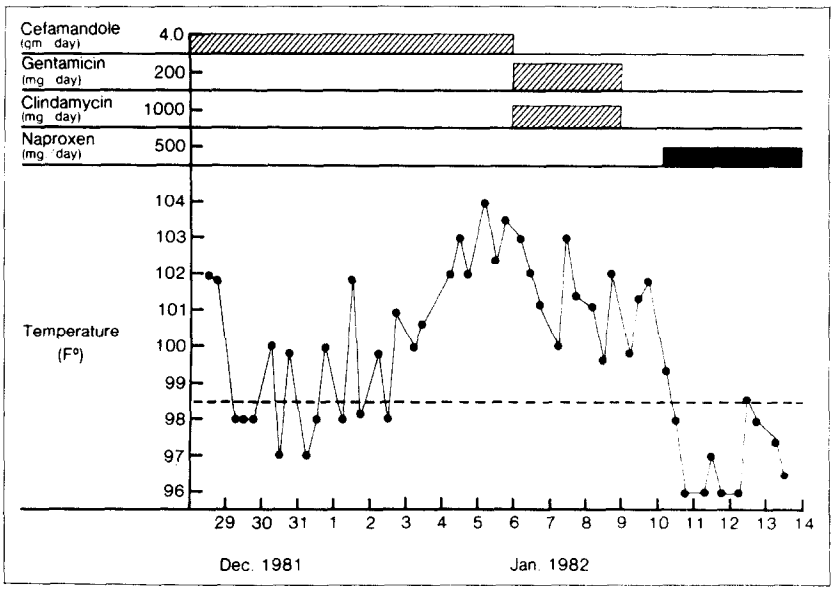

Figure 1. *Febrile course of Patient 13 with neoplastic fever. The patient had a protracted febrile course several weeks and had no significant lysis of fever while receiving antibiotics, but had a response to naproxen within 12 hours.*

riologic studies and other clinical evaluations should be able to provide the diagnosis; appropriate antibiotics would solve the problem in the majority of cases. However, some patients do not have responses to antibiotics and the infectious cause cannot be identified. In these circumstances, it is crucial to be able to differentiate between infectious fever and neoplastic fever.

In the literature, a differential diagnostic method such as nitroblue tetrazolium test for treatable fever of bacterial infection and fever of nonbacterial cause has been attempted by several investigators [11,12], but it was found to have limited value [13]. Our studies indicate that naproxen may be of great value in the differential diagnosis of infectious fever and neoplastic fever. In addition to specific effect of the drug on neoplastic fever, it is safe and has very few side effects, especially since a trial of the drug needed is less than 36 hours. We have seen that fever that failed to respond to naproxen within 24 hours did not respond after treatment of longer than two days. In addition, our preliminary observation suggests that fever due to infectious disease of nonbacterial origin also does not respond to naproxen. In two patients with the diagnosis of connective tissue disease, the partial response to naproxen was an interesting observation. It tends to support the hypothesis that naproxen is primarily effective in the treatment of neoplastic fever.

The precise pathogenesis of fever is unknown in both infection and neoplastic disease. In infection, endogenous or leukocytic pyrogen is thought to be responsible for fever production by stimulating arachidonic acid release and thereby synthesis of prostaglandin E_2 in the hypothalamus [14,15], and also acts on skeletal muscle to stimulate intralysosomal proteolysis by increasing the production of prostaglandin E_2 [16]. Prostaglandin E_2 is known to have direct pyrogenic effects [17]. Inhibitors of cyclooxygenase, such as indomethacin or aspirin, can prevent the onset of fever by suppressing prostaglandin E_2 synthesis. Naproxen has also been shown to inhibit the synthesis or release of prostaglandins in various animal models [18–21]. However, the lack of the effect of naproxen on infectious fever and the specific activity against neoplastic fever suggest the antipyretic action of naproxen may be mediated by a mechanism different from that of other antipyretic agents, and also support the hypothesis that the mechanism of febrile reaction in neoplastic fever is quite different from that of infectious disease. If naproxen, with further extensive clinical studies, were proved to be specific for the induction of lysis of neoplastic fever, research on the action of this drug might be able to provide a clue to the mechanism of neoplastic fever.

The differential diagnosis of unexplained fever in patients with cancer remains one of the most challenging exercises of medical knowledge and clinical oncology practice. In most cases, a careful, intellectual, and organized approach will provide the solution to the problem. Naproxen appears to be a new, additional tool in assisting in the differential diagnosis of infectious fever and neoplastic fever in difficult circumstances, and may prove to be an effective therapeutic and occasionally timesaving and lifesaving drug.

REFERENCES

1. Petersdorf RG, Beeson PB: Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961; 40: 1–30.
2. Molavi A, Weinstein L: Persistent perplexing pyrexia: some comments on etiology and diagnosis. Med Clin North Am 1970; 54: 379–396.
3. Jacoby GA, Swartz MN: Fever of undetermined origin. N Engl J Med 1973; 289: 1407–1410.
4. Wolff SM, Fauci AS, Dale DC: Unusual etiologies of fever and their evaluation. Annu Rev Med 1975; 26: 277–281.
5. Cashman TM, Starns RJ, Johnson J, Oren J: Comparative effects of naproxen and aspirin on fever in children. J Pediatr 1979; 95: 626–629.
6. Goldie IF, Gunterberg B, Tiselius P: An objective evaluation of naproxen for the inflammatory reaction in the rheumatoid hand: a clinical, thermographic and volumetric study. Scand J Rheumatol 1974; 3: 161–168.
7. Melton JW III, Lussier A, Ward JR, Neustadt D, Multz C: Naproxen vs aspirin in osteoarthritis of the hip and knee. J Rheumatol 1978; 5: 338–346.
8. Bowers DE, Dyer HR, Fosdick WM, et al: Naproxen in rheumatoid arthritis: a controlled trial. Ann Intern Med 1975; 83: 470–475.
9. Keinänen-Kiukaanniemi K, Smilä S, Kouvalainen K: Oral antipyretic therapy evaluation of the propionic acid derivatives ibuprofen, ketoprofen, fenoprofen and naproxen. Padiatr Padol 1980; 15: 239–244.
10. Roszkowski AP, Rooks WH, Tomolonis AJ, Miller LM: Anti-inflammatory and analgesic properties of d-2(6′methoxy-2′-naphthyl)-propionic acid (naproxen). J Pharmacol Exp Ther 1971; 179: 114–123.
11. Park BH, Fikrig SM, Smithwick EM: Infection and nitroblue tetrazolium reduction by neutrophils: a diagnostic aid. Lancet 1968; II: 532–534.
12. Feigin RD, Shackelford PG, Choi SC, Flake KK, Franklin FA Jr, Eisenberg CS: Nitroblue tetrazolium dye test as an aid in the differential diagnosis of febrile disorders. J Pediatr 1971; 78: 230–237.
13. Chang JC, Appleby J, Bennett JM: Nitroblue tetrazolium test in Hodgkin's disease and other malignant lymphomas. Arch Intern Med 1974; 133: 401–403.
14. Bernheim HA, Gilbert TM, Stitt JT: Prostaglandin E levels in the third ventricular cerebrospinal fluid of rabbits during fever and changes in body temperature. J Physiol (Lond) 1980; 301: 69–78.

15. Dinarello CA, Bernheim HA: Ability of human leukocyte pyrogen to stimulate late brain prostaglandin synthesis in vitro. J Neurochem 1981; 37: 702–708.
16. Baracos V, Rodemann HP, Dinarello CA, Goldberg AL: Stimulation of muscle protein degradation and prostaglandin E_2 release by leukocyte pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. N Engl J Med 1983; 308: 553–558.
17. Milton AS, Wendlandt S: Effects on body temperature of prostaglandins of the A, E and F series on injection into the third ventricle of unanesthetized cats and rabbits. J Physiol (Lond) 1971; 218: 325–336.
18. Awouters F, Niemegeers CJ, Lenaerts FM, Janssen PA: Delay in caster oil diarrhoea in rats: a new way to evaluate inhibitors of prostaglandin biosynthesis. J Pharm Pharmacol 1978; 30: 41–45.
19. Csapo AI, Henzl MR: The mechanism of naproxen action in parturient rats. Prostaglandins 1977; 14: 799–802.
20. Csapo AI, Csapo EF, Fay E, Henzl MR, Salau G: The role of estradiol 17β in the activation of the uterus during premature labor and the effect of naproxen, an inhibitor of prostaglandin synthesis. Prostaglandins 1973; 3: 839–846.
21. Segre EJ: Naproxen sodium (anaprox): pharmacology, pharmacokinetics and drug interactions. J Reprod Med 1980; 25: 222–225.