The Effect of Naproxen on Fever in Children With Malignancies

SYED K. AZEEMUDDIN, MD,* ROGER A. VEGA, MD,† TAE H. KIM, MD,‡ AND ABDELSALAM H. RAGAB, MD§

Naproxen was used as an antipyretic agent in febrile pediatric cancer patients with evidence of active malignant disease. Sixteen children with leukemia and lymphoma who had fever for more than 72 hours were given naproxen to control fever. Their ages ranged from 16 months to 17 years. There were ten female and six male patients. Their temperature was >38.3°C and the leukocyte count ranged from 400/μl to 33.3 × 10^3/μl, with an absolute neutrophil count (ANC) from 0 to 4514/μl. The children had no evidence of infection by clinical or laboratory evaluations. All patients were receiving triple antibiotics when naproxen was started. Fourteen patients responded to naproxen with complete lysis of fever within 6 hours of initiation of treatment. Two patients did not respond to naproxen, but proved to have culture-positive infections. There were no side effects from the drug. Naproxen is an effective antipyretic in patients with cancer. It may be useful as a means of differentiating fever secondary to active malignant disease from that due to infection.

Cancer 59:1966–1968, 1987.

FEVER WITH NEUTROPENIA is a common problem for cancer patients during chemotherapy.[1] The cause of fever may be infectious or noninfectious.[2] Infection may occur because of alteration of mucosal barriers, myelosuppression, or alteration of phagocytic response.[3] Febrile neutropenic cancer patients usually are admitted to the hospital for systemic cultures and broad-spectrum antibiotics until the results of cultures are known. Fever may not be due to bacterial or viral infections, however, but to the malignancy itself.[4] The incidence of "fever of unknown origin" in children with cancer without proven infection is 60%.[2] The possibility of infection increases when the absolute neutrophil count falls below 200/μl. Patients in remission, however, do not have the same incidence of infection as patients with active malignancy despite low ANC.[4] In contrast, some investigators report an incidence of infection in 55% to 70% of patients with fever and neutropenia and recommend aggressive management of these patients.[2,4] The issue is not clear, however, and many patients are being treated with antibiotics when there is no evidence of infection.

Naproxen is a nonsteroid antiinflammatory drug with analgesic and antipyretic properties. It has been used in the treatment of arthritic conditions and also may be used as an antipyretic agent. We investigated the antipyretic effect of naproxen in cancer patients to evaluate its efficacy in differentiating neoplastic fever from infectious fever.

Patients and Methods

Sixteen children with newly diagnosed malignancies or in relapse, all with active disease, who had fever of undetermined origin, were treated with naproxen. All patients were treated with broad spectrum antibiotics (carbenicillin, oxacillin and gentamicin), and their temperatures were recorded every four hours. After 72 hours of persistant fever despite adequate antibiotic coverage and negative cultures, the patients were treated with naproxen. Naproxen was given if the following criteria were met: (1) temperature greater than 38.3°C (2), duration of fever for 72 hours (3), no evidence of infection on clinical and laboratory examination and (4), negative chest roentgenogram. The naproxen dosage was 7.5 mg/kg/dose at 12-hour intervals. Naproxen was continued for 7 days. The drug was stopped in those patients who did not defervesce.

Results

Table 1 shows that 14 of 16 patients responded to naproxen within 6 hours of initiation of treatment. None of the fourteen patients had culture-proven evidence of infection. The temperature was maintained between 36.7°C

From The Division of Hematology/Oncology, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia.

Supported in part by the CURE organization of Georgia and NIH grant CA20549.

Dr. Ragab is the recipient of a faculty research award from the American Cancer Society.

* Fellow.

† Assistant Professor.

‡ Associate Professor.

§ Professor and Director.

Address for reprints: Roger A. Vega, MD, Division of Hematology/Oncology, Department of Pediatrics, Emory University School of Medicine, 2040 Ridgewood Drive NE., Atlanta, GA 30322.

The authors thank Mrs. Suzan Ingber for typing this manuscript.

Accepted for publication January 6, 1987.

TABLE 1. Clinical Characteristics of Patients

Patient no.	Diagnosis	Age (years)	Duration of fever (days)	Maximum temperature (°C)	Leukocyte count (μl)	Absolute granulocyte count/mm²	Source of infection
1	ALL	3	14	39.4	28,400	0	None detected
2	ALL	12	14	40	33,300	0	None detected
3	ALL	2	21	40	7,000	1540	None detected
4	ALL	10	7	40	3,300	0	None detected
5	ALL	10	7	39.2	16,000	64	None detected
6	ALL	1	7	39.4	1,200	0	None detected
7	ALL	14	7	40.6	13,000	0	None detected
8	ALL	9	7	40	400	0	None detected
9	AML	12	12	40	1,100	22	None detected
10	AML	17	14	39.4	1,100	44	None detected
11	AML	8	14	39.4	1,400	462	Fungal esophagitis
12	APL	10	14	39.2	800	0	Rectal abscess
13	CML	4	7	39.4	5,800	3027	None detected
14	NHL	6	14	39.4	1,900	605	None detected
15	NHL	15	14	40	400	320	None detected
16	IS	17	18	40.6	6,100	4514	None detected

NOTE: ALL: acute lymphocytic leukemia; AML: acute myelocytic leukemia; APL: acute promeylocytic leukemia; CML: chronic myelogenous leukemia in blast crisis; NHL: non-Hodgkin's lymphoma; IS: immunoblastic sarcoma.

and 37.8°C and Naproxen was continued for 7 days. Two patients who did not respond had a culture proven infections. One patient had fungal esophagitis and the other had a rectal abscess. The culture grew *Escherichia coli* organisms.

The course of a patient with immunoblastic sarcoma is shown in Figure 1. This patient did not respond to antibiotic therapy but had complete lysis of fever when naproxen was started. The temperature dropped to 35.6°C within 6 hours of initiation of treatment and then was maintained between 36.7°C and 37.8°C. Naproxen was used for a total of 7 days.

Discussion

Naproxen is used rarely in pediatric patients as an antipyretic agent. It has been used in adult cancer patients, however, as an antipyretic agent to differentiate fever due to cancer from infectious causes.[5] Cashman *et al.*[6] studied the antipyretic effectiveness of naproxen compared with aspirin and a placebo. The results showed that naproxen was more effective than aspirin.[6]

Some of the complications associated with naproxen therapy include gastrointestinal hemorrhage, especially in patients with a previous history of peptic ulcer. The mechanism of the bleeding is most probably related to platelet dysfunction.[7–9] Nephritis has been reported by the manufacturer to occur in laboratory animals that are exposed to the drug over a prolonged period of time. Liver dysfunction manifested by alteration in serum glutamic pyruvic transaminase (SGPT) level has been reported by the manufacturer in less than 1% of cases. Hematologic toxicity eosinophilia, granulocytopenia, leukopenia, and thrombocytopenia has also been reported. Fifty percent of the absorbed methotrexate is reversibly bound to plasma proteins. Nonsteroid antiflammatory drugs displace other drugs from the plasma-protein-binding site. Methotrexate toxicity may be increased greatly, and several deaths have been reported when these drugs were used together. In our small group of patients, naproxen was given at a dose of 7.5 mg/kg every 12 hours. We did not observe any adverse side effects because the drug was administered for a relatively short period of time (maximum of 7 days). There was no evidence of renal or hepatic toxicity. Naproxen did not adversely affect the neutrophil count, platelet count, or hemoglobin levels.

In patients who showed a complete response, (the cultures were negative) the antibiotics were stopped, and they were discharged when they were afebrile for 24 hours without antibiotics. This reduced the number of days the patient was hospitalized. In our study there was complete lysis of fever 6 hours after initiation of naproxen in all but two patients. In those two patients a source of infection was identified, and was treated appropriately with antimicrobial agents.

The precise mechanism of fever in patients with cancer is not known. It is known that many antipyretics act by inhibiting the synthesis of prostaglandin E^2.[10] It is not known, however, if this is the mechanism by which naproxen reduces neoplastic fever. In some children with malignancies, the fever disappears once the granulocyte count exceeds 1000/μl. Since naproxen does not lower fever that is due to infections[5] it may be a useful way to differentiate fever due to infection from that due to the neoplasm. Patients with various malignancies who have negative bacterial cultures and who respond rapidly to

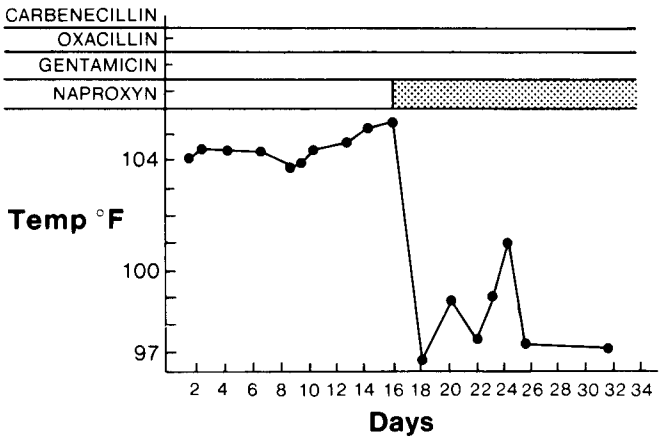

FIG. 1. Temperature curve showing dramatic response to naproxen in a patient with immunoblastic sarcoma. All cultures in the patient were negative for disease.

naproxen may be assumed to have fever due to cancer. In these cases, antibiotic therapy may be stopped if the patient is afebrile and clinically has no signs and symptoms of sepsis. Further studies are needed, however, to document the efficacy of naproxen.

REFERENCES

1. Nachman JB, Honig GR. Fever and neutropenia in children with neoplastic disease. *Cancer* 1980; 45:407–412.

2. Pizzo P. Infectious complications in the child with cancer. *J Pediatr* 1981; 98:341–354.

3. Strauss RR, Paul BB, Jacobs AA, Simmons C, Sbarra AJ. The metabolic and phagocytic activities of leukocytes from children with acute leukemia. *Cancer Res* 1970; 30:480–492.

4. Feigin RD, Shearer WT. Opportunistic infections in children. *J Pediatr* 1975; 87:507–514.

5. Chang JC, Gross HM. Utility of naproxen in the differential diagnosis of fever of undetermined origin in patients with cancer. *Am J Med* 1984; 76:597–604.

6. Cashman TM, Starus R, Johnson J, Oren J. Comparative effects of naproxen and aspirin on fever in children. *J Pediatr* 1979; 95:626–629.

7. Nadell J, Bruno J, Varady J, Segre EJ. Effects of naproxen and of aspirin on bleeding time and platelet aggregation. *J Clin Pharmacol* 1974; 14:176–180.

8. Hart FD, Matts SGF. Naproxen (Naprosyn) and gastrointestinal hemorrhage. *Br Med J* 1974; 2:51–52.

9. Beck E, Hayes-Allen MC. Naproxen (Naprosyn) and gastrointestinal hemorrhage. *Br Med J* 1974; 1:572–573.

10. Dinarello CA, Bernheeim HA. Ability of human leukocyte pyrogen to stimulate late brain prostaglandin synthesis in vitro. *J Neurochem* 1981; 37:702–708.