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## **NSAID test to distinguish between infectious and neoplastic fever in cancer patients**

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**Jae C. Chang, MD**

Fever is a cardinal sign of infection. However, fever has also been observed secondary to such noninfectious conditions as neoplasms, immune disorders, allergic reactions, granulomatous diseases, and inherited diseases.<sup>1,3</sup>

In the majority of febrile patients, an underlying infection can be detected by means of a careful history, physical examination, chest roentgenogram, blood and urine cultures, spinal fluid examination, and other laboratory studies. When fever continues for more than three weeks and extensive investigation fails to uncover the cause, the provisional diagnosis is fever of undetermined origin (FUO).<sup>4</sup>

**COMMON CAUSES OF FUO**—Clinical studies have shown that the most common causes of FUO are infections and neoplasms.<sup>1,3</sup> Unusual infections, such as hidden abscesses, sinusitis, pericarditis, endocarditis, certain fungal diseases, and opportunistic infections, are difficult to diagnose. In certain malignant neoplasms, including Hodgkin's disease, renal cell carcinoma, hepatoma, and even metastatic cancer to the liver, fever may be an initial symptom, without overt manifestation of the primary disease.

**FUO IN CANCER PATIENTS**—Fever is an especially difficult problem in cancer patients, especially when the patient is in the granulocytopenic stage or is immunocompromised after intensive chemotherapy and fever continues despite an acceptable empirical antibiotic regimen.<sup>5-7</sup> Even after extensive clinical and laboratory investigation, the cause of fever cannot be found in 30% to 50% of granulocytopenic patients (granulocyte count < 1,000/ $\mu$ l).<sup>5,8,9</sup> In these patients, the origin of

the fever may be neoplastic.<sup>10,11</sup> Therefore, a means of differentiating between infectious and neoplastic causes of fever is urgently needed to avoid additional antibiotic trials, which are expensive and often unrewarding, and extensive laboratory procedures, which are time-consuming and increase the patient's discomfort and inconvenience.

**THE NSAID TEST**—I have found the administration of naproxen (Naprosyn), a nonsteroidal antiinflammatory drug (NSAID), to be very useful in differentiating between fevers of infectious and of neoplastic origin. In an evaluation of about 70 patients with FUO, naproxen in a dosage of 250 to 375 mg twice a day showed no antipyretic effect in 14 patients against fever that was ultimately found to be infectious.<sup>10,12</sup> However, the same regimen returned temperature to normal within 12 hours in almost all other patients with fever that was finally determined to be neoplastic.<sup>10,12</sup> I have not observed this specific differential property in other antipyretics, such as acetylsalicylic acid and acetaminophen, or in corticosteroids.<sup>13</sup>

My experience over seven years confirms naproxen's value in differentiating between infectious and neoplastic fever. Further, the afebrile state is sustained as long as patients are maintained on the drug. Other investigators have also found naproxen,<sup>14,15</sup> and also indomethacin (Indocin),<sup>16</sup> to be of value in controlling neoplastic fever.

For long-term use, naproxen's side effects, which include gastrointestinal irritation (sometimes leading to gastric ulcer and hemorrhage) and antiplatelet effects, are considerable and can be serious. However, for short-term use, as in the NSAID test, no serious side effects have been encountered.<sup>10-12</sup> The test should be applied cautiously, however, if the patient has thrombocytopenia with a platelet count of less than 30,000/ $\mu$ l.

**FINDING THE CAUSE OF FUO IN CANCER PATIENTS**—Evaluation of FUO in cancer patients should include clinical history, physical examination, and laboratory and radiographic studies. A CBC, urinalysis, blood cul-

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tures (three at 15- to 20-minute intervals), and cultures of urine, sputum, stool, aspirated body fluids, and discharges from local lesions should be obtained. Chest roentgenography, computed tomography, bone marrow examination, and spinal puncture should be performed when appropriate. As soon as culture specimens have been obtained, a seven-day empirical antibiotic regimen covering the broad spectrum of bacterias should be initiated while laboratory results are awaited. Once the pathology or microorganism is identified, the regimen should be modified as necessary to provide maximum effectiveness.

If antibiotic therapy results in clinical improvement and lysis of fever without the fever's origin having been identified, the presumptive diagnosis is infectious fever. In such cases, antibiotic therapy is continued for an appropriate length of time and an investigation for the source of infection is carried out.

If the patient shows no clinical response and continues to be febrile after a seven-day empirical trial of antibiotic and the cause has not been identified, the NSAID test is recommended. Naproxen, 375 mg every 12 hours, is given for 48 hours. (The antibiotic regimen may be continued during this time.) If complete lysis of fever occurs, a strong presumptive diagnosis of neoplastic fever is established and naproxen therapy can

be continued for seven to ten days to control the fever. Clinical improvement should be closely monitored to rule out the possibility of a false response.

If the NSAID test fails to lyse the fever and if noninfectious causes, such as drugs, chemotherapy, and transfusion, have been ruled out, infectious fever unresponsive to antibiotics is presumed, and the patient should be further investigated for an unusual infection, such as a hidden abscess.

**CONCLUSION**—The NSAID test is simple and, if used and interpreted properly, may help to relieve the patient's discomfort, hold down medical expense, and alleviate the physician's stress. More important, the test may prove lifesaving in certain circumstances. Negative NSAID test responses in several patients with FUO have led me to investigate more vigorously (including performing laparotomy) for hidden infections and to uncover serious ones, such as multiple fungal abscesses and infected intraabdominal fistula. Further clinical trials are needed. **FGM**

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