When is a clinical event an adverse drug reaction?

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The reliability of data on drug-induced disease depends on the establishment of a cause-and-effect relation between the drug and the unwanted clinical event. Even when suspected drug reactions are assessed by clinical pharmacologists there is often disagreement as to the certainty about whether the event was drug-induced.[1,2] According to Feinstein[3] the evaluation of adverse drug reactions depends on the "vagaries of clinical judgment of an array of unstandardized physicians". The following case history illustrates the problems of identifying unusual or previously unreported adverse drug reactions.

Case report

A 58-year-old woman was hospitalized four times for investigation of fever. Twenty years previously she had undergone hysterectomy for carcinoma of the cervix; at that time several lipomas were removed from her breast and shoulders. Eighteen years later she suffered a myocardial infarction and subsequently had a three-vessel aortocoronary bypass operation to relieve drug-resistant angina pectoris. A year later cervical spondylosis was diagnosed and naproxen (Naprosyn®), 250 mg orally twice daily, was prescribed.

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First admission

Naproxen therapy was continued for a year, until the woman was hospitalized for investigation of persistent fever. Although no site of infection was identified a 2-week course of antibiotics was prescribed. The patient became afebrile some time after admission. Several blood cultures yielded no organisms, and the results of routine hematologic investigation, chest roentgenography and urinalysis were normal. When she was discharged from hospital naproxen therapy was resumed. A persistent fever again developed; a course of cephalothin had little benefit.

Second admission

Two months after the first admission the woman was again hospitalized for investigation of daily episodes of fever and chills accompanied by myalgia, malaise and epigastric discomfort. Naproxen was discontinued at the time of admission, and the patient remained afebrile throughout her 2-week stay. The hemoglobin concentration was 14.0 g/dL and the leukocyte count was 8.2×10^9/L, with 75% neutrophils, 15% lymphocytes, 4% band forms, 3% eosinophils, 2% monocytes and 1% basophils. The erythrocyte sedimentation rate (ESR) was 57 mm/h. A fluorescent antinuclear antibody test was positive at a dilution of 1:64 and showed a homogeneous pattern; a test for antinative deoxyribonucleic acid (DNA) activity was negative. The serum glutamic oxaloacetic transaminase (SGOT) and serum alkaline phosphatase values were normal. Naproxen therapy was resumed at the time of discharge from hospital.

Third admission

Episodic fever, chills and myalgia prompted admission to hospital again, a month after the second admission. Naproxen was discontinued, and 4 days later the patient became afebrile. A grade 2/6 ejection-type systolic murmur maximal over the apex and radiating to the left axilla was noted. A tuberculin skin test was negative. The abnormal laboratory values were as follows: ESR 110 mm/h, SGOT 55 U/mL (normal less than 35 U/mL), γ-glutamyl transpeptidase 159 IU/L (normal less than 30 IU/L) and serum alkaline phosphatase 504 mU/mL (normal 30 to 120 mU/mL). A fluorescent antinuclear antibody test was positive at a dilution of 1:256 and showed a mixed pattern. Tests for smooth muscle antibody were positive, but those for antimitochondrial antibody were negative. Liver biopsy revealed noncaseating granulomas and an infiltrate of plasma cells and eosinophils in the peripheral lobules.

The patient was challenged twice with short courses of naproxen (Fig. 1). On the 10th hospital day she was given naproxen, 250 mg orally every 6 hours for 24 hours. She promptly became febrile and complained of chills, profuse sweating, weakness, myalgia and polyarthralgia. The symptoms disappeared after her temperature returned to normal 3 days after the last dose of naproxen. On the 15th hospital day naproxen, 250 mg orally every 6 hours for 30 hours, again produced a fever and constitu-

tional symptoms. As before, the temperature returned to normal and the patient became asymptomatic 2 days after the last dose of naproxen.

When the patient was discharged from hospital after a 3-week stay the γ-glutamyl transpeptidase value had decreased to 28 IU/L and the serum alkaline phosphatase value had decreased to 100 mU/mL. A fluorescent antinuclear antibody test was positive at a dilution of 1:16 and showed a mixed pattern; a test for antinative DNA activity was again negative. When the patient was seen 1 month later as an outpatient the ESR was elevated at 77 mm/h, the γ-glutamyl transpeptidase value was still 28 IU/L, the serum alkaline phosphatase value was 104 mU/mL and a fluorescent antinuclear antibody test was negative.

Fourth admission

The patient was readmitted to hospital 6 months after her third admission with a 4-week history of intermittent fever and rigors. She was taking only hydrochlorothiazide and chloral hydrate. She had been treated with cephalexin, tetracycline and chloramphenicol as an outpatient, with no apparent benefit. Her temperature at the time of admission was 38.5°C. There were no new physical findings. A tuberculin skin test was again negative. The hemoglobin concentration was 11.8 g/dL, the leukocyte count 11.8 × 10^9/L, with 75% neutrophils, 16% lymphocytes, 4% monocytes, 3% eosinophils and 2% band forms. The γ-glutamyl transpeptidase value was 22 IU/L and the serum alkaline phosphatase value was 135 mU/mL. A fluorescent antinuclear antibody test was positive at a dilution of 1:16 and showed a homogeneous and speckled pattern. No organisms were cultured from stool, urine or blood. A liver biopsy revealed noncaseating granulomas. Direct stains of the liver tissue and cultures for *Mycobacterium tuberculosis* and fungi were negative. The patient's temperature continued to fluctuate between 37.5°C and 39°C, and it remained elevated even after discontinuation of hydrochlorothiazide and chloral hydrate. Prednisone, 10 mg orally every 6 hours, was given, and the patient's temperature returned to normal 8 days later. She was discharged from hospital with an occasional low-grade fever; the results of liver function tests were unchanged. The daily dose of prednisone was slowly decreased over the next 6 months, and the SGOT and serum alkaline phosphatase values remained normal during this time.

Discussion

Evaluation of suspected adverse drug reactions is particularly difficult when the adverse effect is rare and does not reflect the known pharmacologic actions of the drug. Ibufenac was the first to be used therapeutically of a series of compounds known as the phenylalkanoic acids, of which naproxen is a member. Liver dysfunction was a relatively common adverse effect of ibufenac therapy,[4] but it has been much less frequently reported with other members of the series such as naproxen[5] and ibuprofen.[6,7] In none of these cases was granulomatous hepatitis observed. Although there are several reports of fever due to ibuprofen,[6-8] naproxen-induced fever has not previously been reported. Also, naproxen-induced antinuclear antibodies and lupus erythematosus have not been described.[9,10]

The types of evidence that support a link between a drug and an untoward clinical event[11] can be applied to the patient I have described as follows:

1. There was a plausible temporal sequence between administration of the drug and the event: fever, liver dysfunction and positive results of fluorescent antinuclear antibody tests developed while she was taking nap-

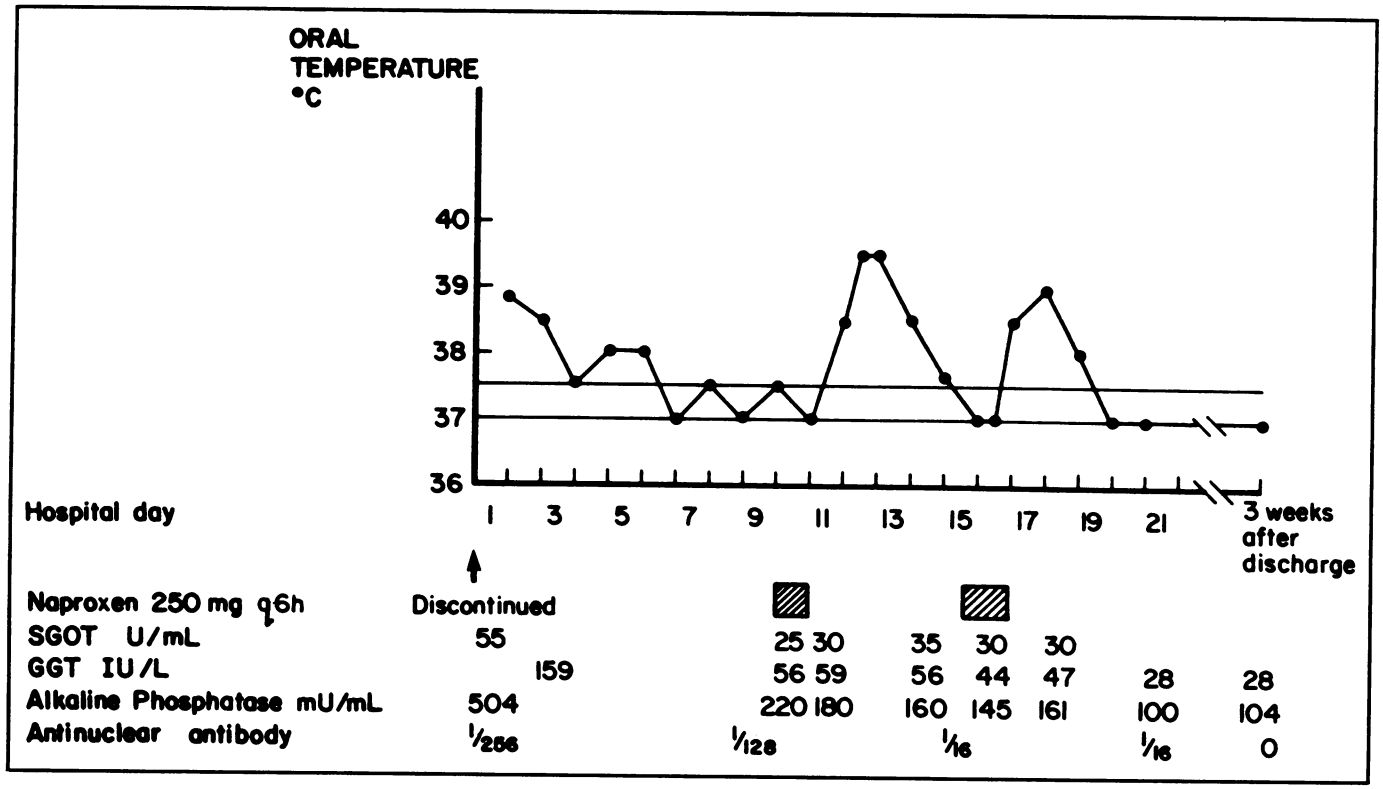

FIG. 1—Responses to naproxen challenges. SGOT = serum glutamic oxaloacetic transaminase; GGT = γ-glutamyl transpeptidase.

roxen. This type of evidence is circumstantial and by itself is insufficient to firmly support an association between the drug and the event.

2. There was improvement when the drug was discontinued. The amelioration of fever, liver dysfunction and positive results of fluorescent antinuclear antibody tests with the discontinuation of naproxen supported the idea that these problems were drug-induced.

3. The event recurred when the patient was re-exposed to the drug. Two challenges with naproxen produced fever that settled 2 to 3 days later, but there were no clear-cut concomitant changes in the results of liver function and antinuclear antibody tests (Fig. 1).

4. Other causes for the untoward clinical event were excluded. This is made difficult by the nonunique nature of adverse drug reactions, so that disease states mimic adverse drug reactions and vice versa. The diagnosis of systemic lupus erythematosus was seriously entertained in this case since fever, liver dysfunction and raised titres of antinuclear antibody are all manifestations of that disorder. However, the antinative DNA antibody test was repeatedly negative, and granulomatous hepatitis is not a feature of systemic lupus erythematosus.[12] Relatively common causes of granulomatous hepatitis such as tuberculosis and fungal infection[13] were excluded by the negative results of culture of blood, urine and liver tissue. Fever and granulomatous hepatitis may both be features of sarcoidosis,[13] but the diagnosis of sarcoidosis cannot be conclusively made when there is evidence of granulomatosis apparently involving only one organ.[14] Several drugs — sulfonamides, penicillin, allopurinol, phenylbutazone, halothane and hydralazine — have been incriminated as a cause of granulomatous hepatitis,[13] but none of these were prescribed for the patient.

The one drawback in blaming naproxen for the fever, liver dysfunction and positive fluorescent antinuclear antibody tests in the patient I have described is that these problems recurred while she was not taking the drug. Fauci and Wolff[13] fully investigated 24 patients with prolonged recurrent fever and granulomatous hepatitis, and could find no cause for these disorders in 21. The condition of the patients with idiopathic granulomatous hepatitis described by Fauci and Wolff and the patient described in my report improved while they were receiving systemic corticosteroid therapy. Perhaps the patient had idiopathic granulomatous hepatitis, and then fever developed when naproxen was given. The inconclusive nature of this case report emphasizes the difficulties of obtaining irrefutable evidence linking a drug to an untoward clinical event.

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