Hepatotoxicity Associated With Acetaminophen Usage in Patients Receiving Multiple Drug Therapy for Tuberculosis*

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We report three patients who experienced hepatotoxic reactions in association with acetaminophen ingestion while undergoing treatment for active tuberculosis with isoniazid, rifampin, and other agents. All were young adult women. One patient intentionally took a large amount of acetaminophen and had typical signs and symptoms of acetaminophen overdosage; another took acetaminophen in combination form for a minor upper respiratory illness. She experienced no symptoms. The remaining patient took acetaminophen to ameliorate the symptoms of fever and malaise that were subsequently attributed to tuberculosis. She had the rapid onset of signs and symptoms of isoniazid hepatotoxicity. The patterns of liver function abnormalities were similar: each patient experienced pronounced serum elevations of hepatocellular enzymes with at most only modest rises in those of bilirubin. All antituberculous drugs were withheld until symptoms resolved and laboratory values became normal; then treatment for tuberculosis was resumed without isoniazid and was successfully completed in all three patients. These cases plus similar reports in the literature suggest that isoniazid or rifampin, or both, may potentiate the hepatotoxicity of acetaminophen, perhaps by induction of cytochrome P450 isozymes that oxidize acetaminophen to its toxic metabolites. ***(Chest 1994; 105: 408-11)***

ALT = alanine aminotransferase; AST = aspartate aminotransferase

Hepatotoxicity is a well-known side effect of drugs used for tuberculosis treatment and prophylaxis. Isoniazid, the historic mainstay of drug therapy against tuberculosis, was determined to be hepatotoxic soon after its introduction,[1,2] and this propensity has been an impediment to its use, particularly as preventive therapy for individuals who are not ill.[3-5]

Acetaminophen, a widely used analgesic and antipyretic drug, also has hepatotoxic potential, mainly when taken in supratherapeutic amounts, such as with intentional or unintentional overdosing.[6] Recently it has been proposed, on the basis of two reports,[7,8] that there may be an interaction between isoniazid and acetaminophen that results in a more severe hepatotoxicity than that which would be expected when either drug is taken alone. Furthermore, rifampin, of equal importance to that of isoniazid in the modern chemotherapy of tuberculosis, seems to potentiate the hepatotoxicity of isoniazid.[9,10]

Recently, we have observed hepatotoxic reactions in temporal association with acetaminophen ingestion in three individuals who were receiving therapy with isoniazid and rifampin, in addition to other agents, for active tuberculosis. We report these cases in order to extend information on a possible adverse interaction between acetaminophen and antituberculosis drugs and to offer a hypothetical mechanism for the synergistic hepatotoxicity of isoniazid, rifampin, and acetaminophen.

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Case Reports

Case 1

A woman born in 1960, had been receiving treatment for drug-resistant tuberculosis with isoniazid, rifampin, pyrazinamide, and streptomycin since her immigration from the Philippines in December 1990. In May 1991, she was hospitalized 24 h after ingesting 15 to 20 tablets of acetaminophen (300 mg acetaminophen per tablet); an ingestion of 4.5 to 6.0 g of acetaminophen. She complained of abdominal pain.

On physical examination, the liver was palpable 2 cm below the right costal margin. Admission laboratory values included a prothrombin time of 14.1 s, total bilirubin level of 18.8 micromole/L (1.1 mg/dl); aspartate aminotransferase (AST), 490 U/L; alanine aminotransferase (ALT), 248 U/L; and alkaline phosphatase, 58 U/L. The blood acetaminophen level was 11 μmg/ml.

The admission diagnosis was hepatotoxicity due to acetaminophen overdosage. Administration of antituberculous medications was stopped, and the patient received a course of treatment with N-acetylcysteine, 1.2 g every 4 h for 3 days.

Liver function abnormalities were at their worst 24 to 48 h after admission, with the bilirubin value being 18.8 μmol/L (1.1 mg/dl); prothrombin time, 17.2 s; AST, 1,200 U/L; and ALT, 1,616 U/L. The patient experienced no further symptoms and was discharged on the eighth hospital day. At the time of discharge, the bilirubin level was 6.8 μmol/L (0.4 mg/dl); the prothrombin time, 11.8 s; AST, 23 U/L; ALT, 271 U/L; and alkaline phosphatase, 43 U/L.

Treatment for tuberculosis was resumed 3 days after discharge from hospital, 12 days after the ingestion of acetaminophen. Drugs chosen for further therapy were pyrazinamide, ethambutol hydrochloride,

ciprofloxacin hydrochloride, and capreomycin sulfate. The patient had no further difficulty, and treatment for active tuberculosis was completed in July 1992.

CASE 2

A Filipino woman born in 1949 immigrated to the United States in 1980. In November 1991, she began to receive treatment for tuberculous cervical adenitis with isoniazid, rifampin, pyrazinamide, and ethambutol. Liver function studies at that time were within normal limits.

At a return appointment for a refill of antituberculous medications 30 days later, she had no complaints. However, liver function studies, done routinely after 1 month of treatment with multiple antituberculous drugs, showed serum levels of AST to be 256 U/L and of ALT to be 517 U/L.

Upon receipt of these abnormal laboratory values, the patient was telephoned, advised to discontinue her medication, and to report to the clinic. On interview and examination 3 days later, she was asymptomatic and there were no new physical abnormalities. Liver function studies done on that day showed bilirubin, 5.1 μmol/L (0.3 mg/dl); AST, 299 U/L; ALT, more than 600 U/L; and alkaline phosphatase, 58 U/L. Serologic testing for viral hepatitis showed hepatitis B surface antigen to be negative, antihepatitis B surface antibody to be positive, antihepatitis B core antibody to be negative, and IgM anti hepatitis A antibody to be negative.

In a further interview at that time, the patient stated that for the 4 day period prior to the clinic visit for refill of antituberculous medications, she had taken capsules containing brompheniramine, phenylpropanolamine, and acetaminophen (each capsule containing 500 mg of acetaminophen), approximately two capsules every 4 hours, for symptomatic treatment of an upper respiratory illness.

Hepatic function studies were monitored on a weekly basis for 3 weeks, and laboratory values gradually returned to normal. Thirty days after drugs were withheld, the AST was 39 U/L, and treatment was resumed with rifampin, ethambutol, and pyrazinamide. The patient experienced no further difficulties and completed therapy in September 1992.

CASE 3

This woman, who was born in 1960, was diagnosed with pulmonary tuberculosis in November 1990. Treatment was started with isoniazid, rifampin, and pyrazinamide. On the 8th day of treatment, she became nauseated. The next day she vomited and called her attending physician. Administration of the antituberculous medications was stopped, and she was given a follow-up appointment. At the time of examination 2 days later, the serum bilirubin level was 22.2 μmol/L (1.3 mg/dl) and the AST value was 465 U/L. She was hospitalized for 2 days. Her symptoms of nausea and vomiting improved promptly. Liver function abnormalities, which peaked 6 days after antituberculous drugs were stopped with a bilirubin level of 22.3 μmol/L (1.3 mg/dl) and an AST value of 920 U/L, returned to normal by the 21st day after administration of drugs was stopped.

In late December 1990, 35 days after treatment for tuberculosis was stopped, it was resumed and consisted of rifampin and ethambutol. The patient experienced no further complications and completed therapy in June 1992.

In a specific interview regarding usage of acetaminophen, the patient responded that 3 days prior to presenting for the evaluation that led to the diagnosis of tuberculosis, she began to take acetaminophen, two 300-mg tablets approximately every 6 h, for relief of symptoms of fever, sweats, and malaise. She continued taking acetaminophen at approximately that same frequency for several days after antituberculous treatment was started because she continued to feel poorly. Administration of the acetaminophen was stopped at about the time she noted the onset of symptoms of hepatotoxicity.

COMMENTS

In this report, we described three patients being treated for active tuberculosis who experienced hepatotoxicity in temporal association with the ingestion of acetaminophen. The circumstances were disparate. One patient (patient 1) intentionally took a relatively large amount of acetaminophen; another (patient 2) took acetaminophen in combination form for a minor upper respiratory illness; the remaining one (patient 3) took it in order to ameliorate the symptoms of fever and malaise that were subsequently attributed to tuberculosis.

The patterns of liver function abnormalities were similar in all three patients. All experienced pronounced serum elevations in concentrations of hepatocellular enzymes with at most only modest rises in those of bilirubin. Clinically, however, there were no consistent patterns. Patient 1 had typical signs and symptoms of mild acetaminophen overdosage and patient 3 had those of isoniazid hepatotoxicity. Patient 2 had no symptoms.

These cases were reported to add to the recent reports of patients who experienced hepatotoxicity after taking acetaminophen and isoniazid.[7,8] Since the publication of the first case report by Murphy et al[7] in November 1990, patients followed up by this clinic who experienced hepatotoxicity while receiving antituberculous drugs were asked routinely about recent acetaminophen usage. Among nine such patients, four (the three reported here and one other one with a less well-documented history) reported recent acetaminophen usage.

Murphy et al[7] speculated that hepatotoxicity associated with acetaminophen and isoniazid results from the induction of cytochrome P450 2E1 (CYP2E1), an enzyme implicated in the oxidation of acetaminophen to its putative toxic metabolite, *N*-acetyl-p-benzoquinone imine.[11,12] Those authors hypothesized that greater activity of the induced enzyme could lead to an increased rate of production of cytotoxic metabolites of acetaminophen. Experimental studies in animals have demonstrated that CYP2E1 induction by isoniazid can potentiate acetaminophen toxicity.[13] Studies in normal human subjects, however, suggest that the time course of this interaction may be complex, involving both induction and inhibition.[14,15]

In addition to isoniazid, each of our patients was receiving rifampin, a drug known to induce CYP3A4[16] and CYP2Cmeph.[17] Other cytochrome P450 inducers, such as phenobarbital and ethanol, also apparently potentiate the clinical manifestation of aceteminophen hepatotoxicity.[18,19] Recently, we have obtained evidence that CYP3A4 forms *N*-acetyl-p-benzoquinone from acetaminophen in human liver microsomes.[12] Induction of this P450 isoform by rifampin may therefore represent an additional risk factor for acetaminophen hepatotoxicity.

Hepatotoxicity is an anticipated side effect of multiple drug therapy for tuberculosis and occurs with greater frequency in that setting than during preventive treat-

ment with isoniazid alone, as cited by Steel et al[9] and C. M. Nolan, M.D. (unpublished observations, 1992). Thus, it is possible that any or all of the patients described in this report had liver damage caused by antituberculous drugs and not associated with acetaminophen. For example, in patient 2 elevations of hepatocellular enzymes were detected on routine testing and were not associated with symptoms. Episodes of mild "transaminasemia" are not uncommon early during isoniazid therapy, are usually transient, and do not ordinarily require cessation of the drug.[20] However, the peak AST level of 299 U/L for patient 2 was considerably greater than levels associated with simple isoniazid transaminasemia, which are usually less than 100 U/L.[21]

On the other hand, patient 1 could have had hepatic dysfunction exclusively due to acetaminophen overdosage. Somewhat against this suggestion is the extensive liver dysfunction she experienced, manifested by very high hepatocellular enzyme levels and prolonged prothrombin times, occurring in association with an ingestion of at most only 6 g of acetaminophen, an amount not usually associated with hepatotoxicity. In this respect, patient 1 is very similar to the case reported by Murphy et al.[7]

Finally, it must be pointed out that all three patients were receiving pyrazinamide in their antituberculous drug regimens. Pyrazinamide, an agent related chemically to isoniazid, shares the latter's potential for hepatotoxicity.[22] The clinical hepatotoxicity of pyrazinamide is less well characterized than that of isoniazid, but it has been shown that patients receiving pyrazinamide with isoniazid and rifampin do not experience a greater frequency of hepatitis than those receiving isoniazid and rifampin alone.[23] What role, if any, pyrazinamide plays in the hypothesized interaction between acetaminophen and antituberculous drugs remains to be determined.

Unfortunately, there is at present no way to establish if drug interactions are the cause of hepatotoxicity without challenging patients with the combination of drugs, or at least one of the drugs thought to be the cause of the hepatotoxicity and thereby putting the patients who receive the challenge at some risk. Nevertheless, the temporal association of the episodes of hepatic dysfunction with acetaminophen usage in these three patients is undeniable and at least raises the possibility of an adverse interaction between acetaminophen and antituberculous drugs. Isoniazid and rifampin currently are the two mainstay antituberculous drugs; their joint use, supplemented by that of pyrazinamide, permits the briefest course of therapy and the best chance for cure.[23] With the current resurgence of tuberculosis in the United States, the value of these two agents in the treatment of tuberculosis, particularly in patients with HIV infection, and in the control of tuberculosis in our communities, is unmeasurable. If an interaction exists among acetaminophen and isoniazid or rifampin or both, it must be clarified quickly so that patients receiving treatment for tuberculosis can be advised to refrain from the use of acetaminophen.

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