Severe Liver Injury Due to Phenelzine with Unique Hepatic Deposition of Extracellular Material

HERBERT L. BONKOVSKY, M.D.*
PATRICIA L. BLANCHETTE, M.D.†
ALAN R. SCHNED, M.D.

White River Junction, Vermont
and

Hanover, New Hampshire

Severe acute and chronic hepatic damage occurred in a white man who had taken phenelzine sulfate (Nardil) 45 mg daily for 70 days. Liver biopsy showed a mixed hepatitic and cholestatic pattern with extracellular deposition of a unique homogeneous collagenous substance. Portal cirrhosis developed and has persisted. The patient was found to have a "rapid acetylator phenotype" and a high rate of metabolism of antipyrine. These innate factors may have predisposed to hepatic injury due to phenelzine.

Phenelzine (phenethylhydrazine, Nardil), a substituted hydrazine, is a monoamine oxidase inhibitor used in the treatment of depression [1]. Patients given phenelzine or other similar monoamine oxidase inhibitors may have life-threatening hypertension if they ingest certain amines, or are given vasopressors. Numerous other untoward effects of phenelzine have been reported, the most serious of which is hepatotoxicity, usually of a hepatitic type [2].

The metabolism of hydrazines is thought to involve acetylation and oxidation [1,3]. Some observers have noted a greater clinical response in those patients with a "slow acetylator" phenotype in whom higher concentrations and more prolonged action of the parent compound would be expected [4,5]. It has also been reported that patients with a slow acetylator phenotype may be at greater risk for the more common nonhepatotoxic side effects of phenelzine [4,5]. In contrast, the hepatotoxicity of other hydrazine derivatives, isoniazid and iproniazid, has been attributed to a reactive metabolite formed in the liver from an acetylated product [3]. Hence, patients with a rapid acetylator phenotype may be at greater risk for serious hepatotoxicity from hydrazines.

Herein we describe a man in whom severe acute hepatitis developed while he was taking phenelzine, with unique striking hepatic accumulation of collagenous extracellular material. Resolution of the acute hepatitis was followed by development of bridging fibrosis and eventually portal cirrhosis. Studies of drug metabolism showed that the patient had a "rapid acetylator" phenotype and a high activity of hepatic cytochrome P450-dependent metabolism of antipyrine. These metabolic characteristics may have predisposed to phenelzine-induced hepatitis.

CASE REPORT

On October 20, 1977, phenelzine sulfate (45 mg orally every day) was prescribed to a 59-year-old retired Caucasian grocer with a long history of unipolar affective illness. Two months later, the daily dose of phenelzine was increased to 60 mg. A few days later, the patient felt ill, lost his appetite, and soon thereafter had itching, jaundice, dark urine, and pale stool. The patient was admitted to the hospital where phenelzine was discontinued after he had taken a total of 3.2 g. He denied skin rash, arthralgias, fever, chills, recent blood transfusions, exposure to environmental toxins, or known contact with hepatitis. Alcohol intake averaged

From the Departments of Medicine and Pathology, Veterans Administration Medical Center, White River Junction, Vermont, and the Dartmouth Medical School, Hanover, New Hampshire. This work was supported by research funds from the United States Veterans Administration and by a grant from the National Institutes of Health (HL 28177). Manuscript accepted December 12, 1984.

* Current address and address for reprint requests: Clinical Research Facility, Emory University School of Medicine, 1364 Clifton Road, NE, Atlanta, Georgia 30322.

† Current address: Kuakini Gerontology Center, Kuakini Medical Center, Honolulu, Hawaii.

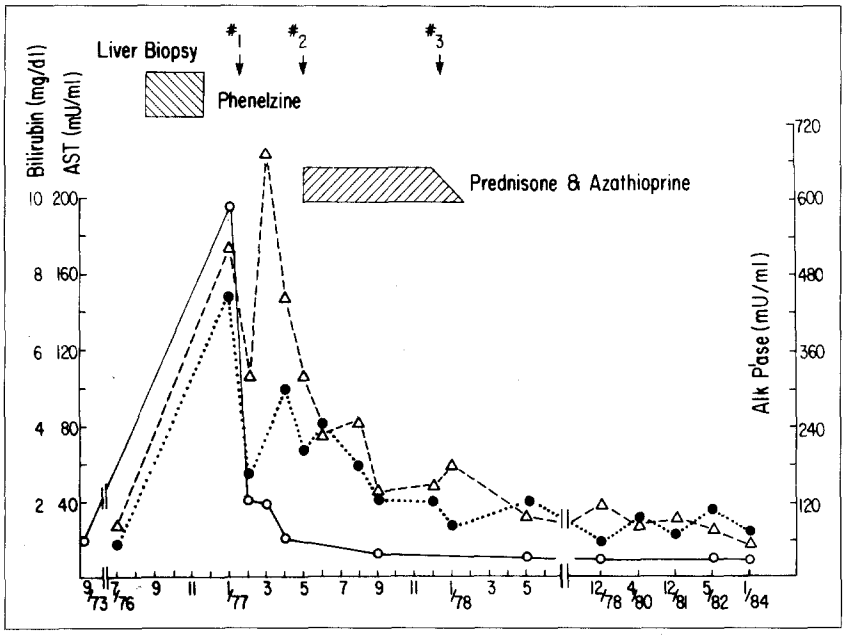

Figure 1. *Time course of biochemical abnormalities and treatment of a patient with acute phenelzine-induced hepatitis progressing to cirrhosis.* ● . . . ● *= serum aspartate transaminase (AST);* Δ - - - Δ *= serum alkaline phosphatase (Alk P'ase);* O — O *= serum bilirubin.*

from none to one and a half ounces daily. He had a 40 pack-year history of cigarette smoking.

For at least one year prior to initiation of phenelzine therapy, the patient had taken daily probenecid, 500 mg, colchicine, 0.6 mg, chlordiazepoxide, 30 mg, and flurazepam, 30 mg. He had no prior history of hepatobiliary or pancreatic disease. Routine examinations performed three years and again one month prior to institution of phenelzine therapy showed no clinical enlargement of liver, other signs of liver disease, or abnormalities in levels of serum alkaline phosphatase, aspartate transaminase, or bilirubin.

Physical examination revealed an alert, afebrile, jaundiced man without spider angiomata. The liver span was 16 cm in the right mid-clavicular line; the edge was slightly tender to palpation. Spleen tip was palpable.

Laboratory investigations showed the following values: white blood cell count, 6,300/mm^3 with a normal differential; no eosinophilia; hemoglobin, 11.9 g/dl; total serum bilirubin, 9.8 mg/dl; the direct-reacting fraction of bilirubin, 9.7 mg/dl; serum aspartate transaminase, 148 mU/mL (normal, 7 to 40); serum alkaline phosphatase, 520 mU/ml (normal, 30 to 85); serum gammaglutamyl transpeptidase, 695 mU/ml (normal, four to 28); no demonstrable hepatitis B surface antigen; total serum protein, 6.8 g/dl; serum albumin, 3.1 g/dl; serum protein electrophoresis showed alpha-1, 6 percent, alpha-2, 13 percent, beta, 17 percent, gamma, 18 percent; serum alpha-fetoprotein was not demonstrable; blood urea nitrogen, 20 mg/dl; serum creatinine, 1.0 mg/dl; serum amylase, 80 mg/dl; serum cholesterol, 559 mg/dl; serum triglyceride, 185 mg/dl; erythrocyte sedimentation rate, 82 mm per hour; prothrombin time 13.4 seconds (control, 12 seconds). **Figure 1** summarizes the course of biochemical changes.

Results of ultrasound of the biliary tree and pancreas were normal. Liver/spleen scanning (technetium-99m-sulfur colloid) showed increased liver and spleen size and inhomogeneous uptake in the liver with increased uptake in the spleen and bone marrow, consistent with generalized liver disease and portal hypertension.

Hepatic injury from phenelzine was suspected. All medications were discontinued and there was gradual improvement. Approximately 20 days after the onset of symptoms, needle biopsy of the liver was performed (see **Figure 2, top left** to **right** and description later). Sigmoidoscopic findings were normal to 24 cm; rectal biopsy showed no amyloid.

After one month of hospitalization, the patient was discharged with clinical and biochemical improvement. Subsequent to discharge, there was a transient increase in serum alkaline phosphatase and aspartate transaminase levels. In April, four months after the onset of symptoms, the patient's liver remained enlarged and firm; there were persistent elevations of serum alkaline phosphatase and aspartate transaminase levels. Repeated liver biopsy was performed (**Figure 2, bottom left**); treatment with prednisone (15 mg daily) and azathioprine (50 mg daily) was begun and continued for seven months. During this time, serum bilirubin, aspartate transaminase, and alkaline phosphatase levels returned to normal (Figure 1). In December 1978, one year after the onset of illness and prior to discontinuation of anti-inflammatory therapy, needle biopsy of the liver was performed a third time (**Figure 2, bottom right**).

In the ensuing six years, the patient resumed all previous medications, except for the phenelzine, without recrudescence of hepatitis or other adverse effect. Serum aspartate transaminase, alkaline phosphatase, and gammaglutamyl transpeptidase levels remain within the normal range. The liver is firm and nontender; its span is 12 cm. The spleen tip is no longer palpable.

Pathologic Study. The first biopsy specimen (Figure 2, top left to right) showed widespread collapse, lobular disarray, portal-portal bridging fibrosis, and regeneration. There were marked bile ductular proliferation, cholestasis, and

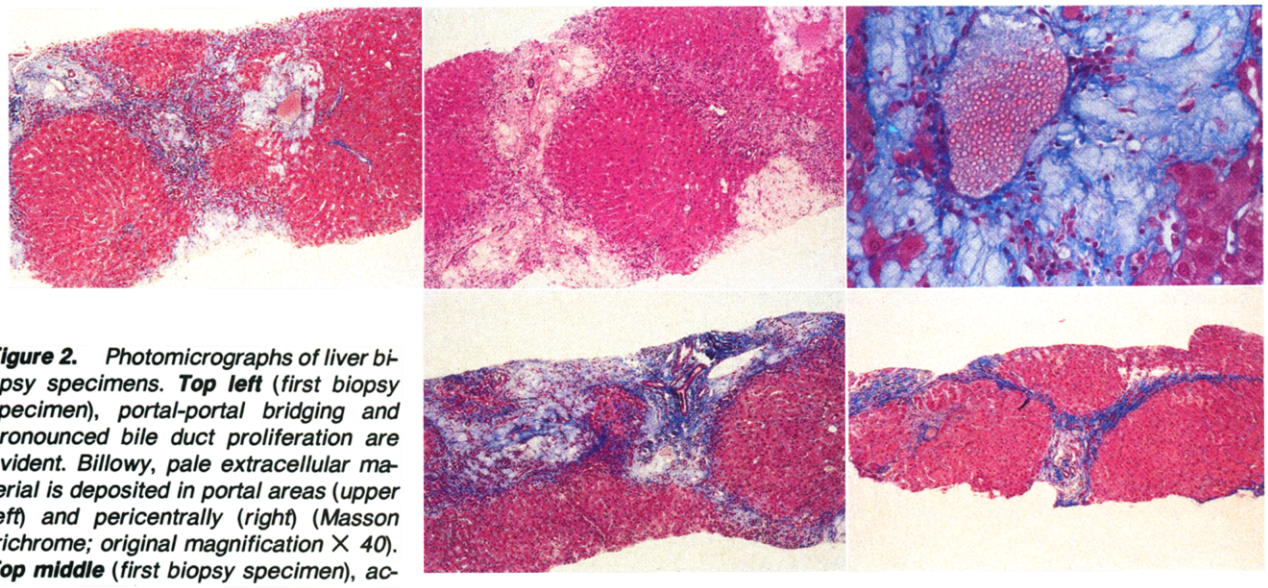

Figure 2. *Photomicrographs of liver biopsy specimens.* ***Top left*** *(first biopsy specimen), portal-portal bridging and pronounced bile duct proliferation are evident. Billowy, pale extracellular material is deposited in portal areas (upper left) and pericentrally (right) (Masson trichrome; original magnification × 40).* ***Top middle*** *(first biopsy specimen), active lobular inflammation is more conspicuous on hematoxylin and eosin-stained section (upper right) (original magnification × 40).* ***Top right*** *(first biopsy specimen), high-power illustration of pericentral extracellular deposit. Note pale, amorphous quality (Masson trichrome; original magnification × 200).* ***Bottom left*** *(second biopsy specimen), progression of portal fibrosis and bridging; extracellular deposits still prominent (Masson trichrome; original magnification × 40).* ***Bottom right*** *(third biopsy specimen), portal bridging is marked, and fibrous septums are contracted and narrowed. Inflammation has subsided, and nearly all amorphous deposits are incorporated into the fibrous bands (Masson trichrome; original magnification × 40).*

mixed portal, periportal, and lobular inflammation. Most striking were the abundant extracellular billowy deposits of pale, homogeneous material, seen predominantly in and around portal areas but occasionally pericentrally as well (Figure 2, top left and right). The material stained pale blue with Masson trichrome for collagen, and was positive with Alcian blue-periodic acid-Schiff stain. The Alcian-blue positivity was diminished by pretreatment of sections with Streptomyces hyaluronidase, indicating that some of the Alcian-blue-positive material was hyaluronic acid. The material was not affected by chondroitinase ABC pretreatment and did not stain with Alcian blue at pH 1, suggesting that the material did not contain suflated mucopolysaccharides. The billowy material did not stain for amyloid.

The second biopsy specimen demonstrated persistence of a mixed inflammatory infiltrate, but with rather denser fibrosis, more advanced bridging, and a suggestion of early nodule formation. The amorphous deposits were still conspicuous (Figure 2, bottom left).

The third biopsy specimen (Figure 2, bottom right) showed cirrhosis, with thin, densely collagenized septums connecting portal areas, reduced inflammation, and less bile ductular proliferation than previously. The amorphous deposits were also less prominent and appeared to be partially incorporated or absorbed into the septal fibrosis.

Tissue from the first biopsy specimen was deparaffinized and examined ultrastructurally. Within an amorphous portal deposit, slender fibrils were detected with a faint cross-striation of approximately 700 Å periodicity. The fibrils were arranged within vague bundles, between which elongated cells resembling fibroblasts were interspersed. This material was believed to represent young or degenerated collagen.

Special Studies. Well after clinical recovery from the active hepatitis, the patient's acetylator phenotype, antipyrine elimination kinetics, and urinary excretion of glycosaminoglycans were determined. These studies were performed after the procedures had been fully explained to the patient and his informed consent had been obtained.

Acetylator phenotype: The patient was found to have a rapid acetylator phenotype as assessed by the ratio of monoacetyldapsone to dapsone in his urine following administration of a test dose of dapsone. The ratio of acetyldapsone to dapsone in the patient's urine was 0.59. By the method used [5], patients with a ratio below 0.3 are classified as "slow acetylators," 0.3 to 0.35 as "indeterminate," and above 0.35 as "rapid acetylators."

Antipyrine metabolism: Hepatic microsomal mixed-function oxidase activity was estimated by the measurement of antipyrine elimination kinetics [6]. The systemic clearance of antipyrine was 4.8 liters per hour (normal range = 2.6 to 4.3 liters per hour), and the half-life of the drug was 6.4 hours (normal range = seven to 17 hours).

Urinary excretion of glycosaminoglycans: A urine specimen obtained 16 months after the onset of hepatitis contained 6.3 μg of glycosaminoglycans (expressed as total uronic acid/mg creatinine). The determination was performed as described previously [7]. This value was higher than the normal range for adult men (2.0 to 4.8 μg uronic acid/mg creatinine), and was in the range previously reported for patients with hepatitis, cirrhosis, or hepatic

angiosarcoma [7]. Further fractionation of the urinary glycosaminoglycans revealed 0.2 as hyaluronate, 1.6 as chondroitin sulfate, and 1.0 as heparin (all values are μg/mg creatinine). These results are similar to those reported previously in other liver diseases [7]. The amounts of liver tissue obtained by needle biopsy in our patient were insufficient to permit quantitative analyses of liver glycosaminoglycans.

COMMENTS

Although our patient received other drugs, the development and evolution of clinical and histologic findings implicate phenelzine as the cause of his severe liver injury. Because of the severity of the hepatitis, we did not believe intentional rechallenge with this drug should be performed.

The unique features of our patient were (1) the striking accumulation of billowy extracellular material in the liver, and (2) the documented progression of disease from severe acute hepatitis, with both "hepatitic" and "cholestatic" features, to portal cirrhosis. This progression occurred despite a course of anti-inflammatory and immunosuppressive therapy that may or may not have affected the evolution of the liver disease.

The billowy extracellular material (Figure 2) was present in large amounts during the acute hepatitic phase and gradually decreased with time. Special stains and electron microscopy indicated that this material contained collagen and glycosaminoglycans, especially hyaluronic acid, although the relative weakness of Alcian-blue staining suggested that most of this material was not glycosaminoglycans. It seems likely that the billowy material mainly represented immature collagen produced by a fibroblastic synthetic response to liver injury. Other cells may conceivably have contributed to its synthesis as well. An alternative suggestion is that it represented myxomatous degeneration of collagen (G. Klatskin, personal communication). In any event, to our knowledge, material of this sort and in this amount has not previously been described in any drug-induced hepatitis nor, indeed, in acute hepatitis of any cause. We speculate that its development related to an unusual interaction between phenelzine and our patient's liver. Much smaller amounts of similar material rarely have been observed in Glisson's capsule or in livers of patients with chronic fibrosis or cirrhosis, especially secondary biliary cirrhosis (G. Klatskin, personal communication).

Hydrazines and the closely related hydrazides are well-known hepatotoxins [2,3]. Indeed, the hydrazide, iproniazid, another monoamine oxidase inhibitor, was removed from the market because of the high frequency with which it caused hepatic injury. The mechanism(s) whereby such agents cause hepatic necrosis and hepatitis remains uncertain, although evidence has been presented for a sequence of events in which drug acetylation gives rise to acetyl-hydrazine, which undergoes further cytochrome P450-dependent metabolism to a highly reactive and toxic intermediate [3]. Our patient had a genetic "rapid acetylator" phenotype, and also had a rapid rate of metabolism of antipyrine, a drug metabolized by the cytochrome P450-dependent hepatic mixed-function oxidase system [6,8]. These innate features of our patient's hepatic drug-metabolizing systems may have made him particularly prone to the development of severe hepatitis due to phenelzine. However, the pathway(s) of metabolism of phenelzine in humans is not established [9,10]. Therefore, the aforementioned scheme presently is only hypothetical. Further studies of acetylator phenotype and mixed-function oxidase activities in other patients with hepatitis due to phenelzine and other hydrazine-containing drugs may help to clarify the biochemical mechanisms that underlie liver injury produced by these agents.

ACKNOWLEDGMENT

Drs. C. Tamburro and C. Kupchella performed urinary determinations of glycosaminoglycans and aided analysis of the liver biopsy specimens by treating with specific hyaluronidase and chondroitinase. Dr. R. Stenger performed electron microscopy of liver tissue. Drs. G. Klatskin and J. Galambos reviewed the liver biopsy findings and provided helpful comments. Dr. M. Reidenburg measured the concentrations of dapsone and acetyldapsone in the urine. Mr. R. Chapman ably typed the manuscript.

REFERENCES

1. Robinson DS, Nies A, Rararis CL, Ives JO, Bartlett D: Clinical pharmacology of phenelzine. Arch Gen Psychiatry 1978; 35: 629–635.
2. Cook GC, Sherlock S: Jaundice and its relation to therapeutic agents. Lancet 1965; I: 175–179.
3. Nelson SD, Mitchel JR, Timbrell JA, et al: Isoniazid and iproniazid: activation of metabolites to toxic intermediates in man and rat. Science 1976; 193: 901–903.
4. Evans DAP, Davison MB, Pratt RTC: The influence of acetylator phenotype on the effects of treating depression with phenelzine. Clin Pharmacol Ther 1965; 6: 430–435.
5. Drayer DE, Reidenberg MM: Clinical consequences of polymorphic acetylation of basic drugs. Clin Pharmacol Ther 1977; 22: 251–258.
6. Anderson KE, Alvares AP, Sassa S, Kappas A: Studies in porphyria V. Drug oxidation rates in hereditary hepatic porphyria. Clin Pharmacol Ther 1976; 19: 47–54.
7. Kupchella CE, Tamburro CH: Urinary and tissue glycosaminoglycan patterns in hepatic angiosarcoma. In: Nieburgs HE, ed. Detection and prevention of cancer, part I, vol 1. New York: Marcel-Dekker, 1977; 915–926.
8. Vesell ES: The value of antipyrine and aminopyrine as model substrates in assessing drug-metabolizing capacity in man. Trends Pharmacol Sci 1980; iv–v.
9. Marshall EF: The myth of phenelzine acetylation (letter). Br Med J 1976; 2: 817.
10. Sanders GL, Rawlins MD: Phenelzine: acetylator status and clinical response. Eur J Clin Pharmacol 1979; 7: 451–452.