Hepatic Injury Caused by
L-Alpha-Methyldopa

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SUMMARY
L-alpha-methyldopa (Aldomet)-induced liver disease is a relatively mild and uncommon complication of therapy with this drug. Most commonly it is characterized by a rise in serum alkaline phosphatase, glutamic oxaloacetic transaminase levels, and increased Bromsulphalein retention. Elevation of the serum bilirubin may occur. In its most benign form the condition is usually symptomless, but complaints, such as anorexia, abdominal pain, or pruritus, and signs, such as fever or hepatomegaly, may occur. Histologic changes similar to those of viral hepatitis have been observed. The condition is usually benign and remits on withdrawal of the drug. Progressively more mild exacerbations on readministration of the drug suggest that desensitization may be possible in patients who exhibit hepatic abnormalities. Its low and sporadic incidence is typical of a hypersensitivity reaction. It is suggested that routine liver function tests should be undertaken at intervals during therapy. The occasional occurrence of Aldomet-induced liver disease is no contraindication to the use of this antihypertensive agent.

Additional Indexing Words:
Liver function tests Drug hepatitis Biochemical changes in serum

Since its introduction in 1960 by Oates and his co-workers,1 L-alpha-methyldopa (Aldomet)* has achieved wide acceptance as an antihypertensive agent. Its advantages include the ability to maintain the reduction of blood pressure while the patient is in the recumbent position and the relative absence of orthostatic hypotension.2 Its use has, however, occasionally been associated with three types of toxic side effects; hematologic disorders,3,4 acute febrile reactions,5-8 and abnormalities of liver function.9-26 Reports of hepatic toxicity, which consist largely of incidental comments, are little known. Popper and his associates,27 for example, in their recent review of drug-induced hepatic disorders do not mention methyldopa-induced liver disease. Although methyldopa-induced liver injury is usually mild and reversible, it is not invariably benign. Zarday and his colleagues28 observed a severe illness resembling viral hepatitis in association with administration of methyldopa to one patient and Perret and co-workers29 described fatal acute massive hepatic necrosis in another.

The purposes of this publication are to describe a patient with proved methyldopa-induced liver disease, to review the published literature, define the clinical syndrome, and to discuss the pathogenesis of this disorder.

Report of Case
A Negro male, aged 37 years, was first investigated for hypertension in 1961. No cause for this condition was found and, until 1967, no treatment was administered. The medical history was negative except for an episode of ulcerative proctitis in 1961 which responded to rectal steroid therapy. He had on several occasions exhibited
urticaria following the administration of phenobarbital, secobarbital, and penicillin. He had not experienced cardiac, renal, or central nervous system disease, or, prior to 1967, any form of liver disease. He drank approximately 1 quart of beer and 3 ounces of whiskey daily.

In January 1967 his blood pressure was 200/120 mm Hg; no other abnormality was present. Treatment was started with Aldomet 500 mg twice daily; no other medication was administered. Within 1 week, abdominal discomfort and diarrhea developed and were soon followed by pruritus and dark urine. There were no skin lesions. During the next 4 months treatment with Aldomet was twice discontinued by his physician; on each occasion pruritus decreased but recurred on reintroduction of the drug. During this period the patient lost 20 pounds. In early April 1967 nausea, vomiting, distaste for cigarettes, and jaundice developed and on April 26 he was admitted to the West Haven Veterans Administration Hospital.

He denied exposure to persons with hepatitis, the ingestion of shellfish, the administration of blood transfusions, or the use of drugs other than Aldomet. He had noted no change in the color of the stools, although pruritus was still present.

Administration of Aldomet was discontinued on admission to hospital. The patient appeared to be in fair health and was fully oriented. The temperature was 100.4°F, and the pulse rate, 84/min. Findings were within normal limits except for a blood pressure of 180/120 mm Hg, scleral icterus, and hepatomegaly. The lower border of the liver, which was slightly tender, was palpable 1 cm below the right costal margin. The spleen was not felt. Spider angioma, palmar erythema, gynecomastia and testicular atrophy were absent.

Biochemical investigation of the serum revealed a large increase in both direct and indirect-reacting bilirubin, marked increase in the serum glutamic oxaloacetic transaminase (SGOT) activity, and minimal elevation of the serum alkaline phosphatase (SAP) (table 1). The serum cholesterol was 340 mg/100 ml. Hematologic examination showed a hematocrit of 49%, a white blood count of 11,500/cu mm, normal differential count and a negative Coombs’ test. Needle biopsy of the liver performed 2 days after admission showed patchy hepatocellular necrosis and regeneration, with mononuclear leukocytic infiltration of the portal tracts, occasional eosinophils, and slight portal fibrosis. There was no cholestasis (fig. 1).

Table 1

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<td>-</td>
<td>-</td>
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<td>Total serum bilirubin (ng/100 ml)</td>
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These findings were considered compatible with viral hepatitis or with drug-induced hepatic injury. The course was benign and the biochemical abnormalities rapidly reverted toward normal. On discharge from the hospital 3 weeks after admission the level of total serum bilirubin had fallen to 1.8 mg/100 ml and that of the SGOT to 67 units/100 ml (table 1). The patient was advised not to drink.

He was readmitted 1 month later, on June 14, to determine through a trial of Aldomet therapy whether or not this drug had caused jaundice. The liver function tests were now normal (table 1), and the concentration of serum cholesterol had fallen to 200 mg/100 ml. Aldomet was administered in a dose of 62.5 mg every 6 hours for four doses, followed by 125 mg every 6 hours for 24 hours, and thereafter by 250 mg three times daily, without change in liver function tests. On this dosage blood pressure decreased to normal levels during the next 3 weeks. No changes were observed in temperature, pulse rate, white blood count, or urine. No abnormality was evident from the liver function tests until July 7, 3 weeks after reintroduction of the drug, when the SGOT and serum alkaline phosphatase were found to be elevated (table 1). Treatment with Aldomet was immediately discontinued, and results of the liver function tests reverted to normal.

It was learned in retrospect that the patient had drunk an excessive amount of beer shortly before his relapse.

Whether the methyldopa or the alcohol had been responsible for the hepatic dysfunction was not clear, and after a period of abstention from alcohol a second trial of Aldomet, in a dose of 250 mg every 8 hours, was commenced on August 4. After 17 days, during which the patient denied any consumption of alcohol, the level of SGOT became slightly elevated. The patient was asymptomatic, and there were no other abnormalities of liver function (table 1). Aldomet therapy was continued in the same dosage for the next 12 weeks, until October 23, during which time SGOT value remained between 60 and 85 units/100 ml. Pruritus was absent throughout. On October 20, the value for SGOT was 65 units/100 ml and the Bromsulphalein (BSP) excretion was 10%. Other liver function tests gave normal results (table 1). A second liver biopsy showed considerable improvement compared with the first. There was now no hepatic cellular necrosis, and regeneration was active (fig. 2). On discontinuing treatment with Aldomet, the SGOT returned to normal within 10 days (table 1). Aldomet was not administered again, and during the subsequent 11 months no abnormality was observed on liver function tests despite resumption of alcohol consumption.

Figure 1

Acute phase of disease (April 1967). Diffuse cellular injury and necrosis and disruption of the normally regular cell plates are evident. The portal area on the right is infiltrated with mononuclear leukocytes.
of drinking. Control of hypertension was later achieved by the use of reserpine, hydralazine, and chlorothiazide.

Discussion

The association of hepatocellular dysfunction with administration of Aldomet, first recorded by Gillespie in 1960,9 has subsequently been observed by many workers.10-26 The patients reported by Zarday,28 Perret,29 and their colleagues have been the most severely affected. Zarday and associates28 reported the case of a 37-year-old man who developed a severe viral hepatitis-like disease after receiving Aldomet for 11 weeks. The disease reached peak severity 10 days after cessation of Aldomet therapy. It is possible that this disease represented coincidental viral hepatitis rather than methyldopa-induced liver injury since readministration of the drug was not attempted. Perret and associates29 described an elderly man who suddenly developed fulminant fatal jaundice after having received Aldomet for several months. Autopsy revealed massive fatty change of the liver with perilobular liver cell necrosis. Here, too, an association between Aldomet and the liver injury was assumed but not proved. The histologic picture in this instance was more indicative of toxic than of viral injury.

In our patient the relationship between Aldomet and liver damage was unequivocally established. Within 1 week of the start of Aldomet therapy gastrointestinal symptoms appeared, followed by jaundice and pruritus; these findings had remitted and recurred on two occasions as the drug was withdrawn and readministered. After withdrawal of Aldomet for the third time severe liver injury resolved within 7 weeks. Challenge with Aldomet on each of two further occasions resulted in mild recurrences of the hepatic disorder; each successive relapse was clinically and biochemically less severe than that preceding it. Horwitz and his colleagues26 demonstrated similar biochemical and histologic exacerbation following challenge with Aldomet in their case. It is conceivable, but unlikely, that relapses of active

Figure 2
Convalescent phase of illness (October 1967). The more normal cellular regularity is evident around central vein on left. Residual portal inflammatory reaction and regenerative activity persist.
viral hepatitis may have spontaneously recurred after each administration of Aldomet. Similarly it cannot be excluded that Aldomet in some way predisposes the patient to the development of intercurrent viral hepatitis or permits the activation of latent hepatitis.

The clinical picture of Aldomet-induced liver injury appears to be clinically, biochemically, and histologically indistinguishable from viral hepatitis. Like viral hepatitis the disorder associated with administration of Aldomet is often clinically silent. In the majority of patients the condition has been entirely asymptomatic and has been detected only as a result of routine liver function tests. Most commonly mild elevations of SGOT or serum alkaline phosphatase have been observed. In such patients histologic examinations of the liver have been reported as normal, in some instances nonspecific abnormalities have been described. In more severe cases the condition resembles typical viral hepatitis. It begins with anorexia, nausea, vomiting, or abdominal discomfort; jaundice may ensue. Fever and hepatomegaly may be present. Histologically the characteristic pattern of viral hepatitis is found. The elevation of serum alkaline phosphatase in association with jaundice, pruritus, and hypercholesterolemia, which suggested the possibility of extrahepatic obstructive jaundice in our patient, probably corresponds to the "obstructive" phase of early viral hepatitis. Conceivably it may represent cholangiolitic hepatitis of the type associated with phenothiazine. Usually the course is benign. Only one fatal case has been described so far, and no instances of postnecrotic cirrhosis have been reported.

The onset of the condition may occur from 1 week to 1 year after Aldomet therapy is started, but most examples, particularly if severe, have occurred during the first 3 months of treatment (also Gates, T.N.: Personal communication to the authors). In mild instances the disorder may persist without progression throughout the period of drug administration; resolution may take place spontaneously even while drug therapy is continued. In the remainder improvement occurs shortly after the discontinuation of Aldomet and is usually complete.

The frequency with which liver disorders are associated with Aldomet therapy is uncertain. The occurrence of altered liver function tests has been described as rare. Only 11 instances of hepatic dysfunction had been detected among the first 1,500 recipients of the drug, an incidence of less than 1%. Subsequent studies in which routine liver function tests have been performed (table 2) revealed that the incidence of abnormal tests varies from 0% to 35% (mean, 6%). Variations in the timing, frequency, and type of biochemical studies probably account for this wide divergence.

These observations raise several points of interest regarding the nature of the hepatic injury induced by Aldomet. Drug-induced hepatic injuries may be classified either as direct hepatotoxicity or as indirectly induced "hypersensitive" hepatic damage. Liver disease caused by direct hepatotoxic drugs is characterized by a predictable and, usually, brief latent period, hepatocellular damage proportional to the dosage of the offending drug, and a uniform histologic picture. It can be elicited in all patients and in other species. On the other hand, indirect sensitization hepatitis, which is neither related to the dosage nor the duration of administration of the drug, varies in its histologic appearance and is frequently accompanied by other signs of hypersensitivity, such as fever, rash, arthralgia, or eosinophilia. It appears in only a small fraction of exposed persons, many of whom have a positive allergic history. It can rarely be reproduced in experimental animals. Readministration of the drug often elicits a prompt exacerbation of liver injury. Zimmerman has suggested that indirect hepatotoxicity need not always be secondary to sensitization but may be associated with specific abnormalities of drug metabolism which may mimic some of the features of hypersensitivity reactions.

The hepatic injury associated with administration of alpha-methyldopa resembles the pattern seen with hypersensitivity reactions. Its incidence is low but variable. The latent
period varies from a few days to several months. The dosage of methyldopa appears irrelevant in precipitation of the disorder.26 The hepatic injury has not been reproduced in experimental animals. It may be associated with fever,5-8 rash14 eosinophilia,5,9 or a positive direct Coombs’ test.8 The histologic pattern observed in these patients varies considerably. Readmission of methyldopa frequently, but not always,16 induces recurrence of the disorders.

It is not possible at present to predict which patients will develop liver disease following the administration of Aldomet. Consequently it seems reasonable to attempt to identify those patients who exhibit liver injury associated with methyldopa at the earliest possible stage. This can most easily be accomplished by using SGOT activity as a screening test for hepatic damage; serial estimations performed every 2 weeks for 6 months will detect the great majority of susceptible patients28 early enough in the course of the disease to permit cessation before serious injury has occurred.

References


10. IRVINE, R. O. H., O’BRIEN, K. P., AND NORTH,

Table 2

Incidence of Hepatic Dysfunction in Detailed Studies with Aldomet

<table>
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