PAPERS AND ORIGINALS

Methyldopa Liver Damage

P. J. TOGHILL, P. G. SMITH, PATRICIA BENTON, R. C. BROWN, H. L. MATTHEWS

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Summary

Twenty patients are described in whom liver damage appeared to be directly related to the administration of methyldopa. Sixteen had hepatitic syndromes from which they recovered on stopping methyldopa; four of these patients had recurrences of jaundice after a second course of the drug. Features suggestive of active chronic hepatitis were found in two patients. There were two deaths attributed to methyldopa, one of these being in a patient with pre-existing undiagnosed macronodular cirrhosis.

Introduction

For some years there have been reports of hepatic damage in patients taking methyldopa. The clinical syndrome has usually shown similarities to viral hepatitis with prompt recovery on stopping treatment (Elkington *et al.*, 1969; Tysell and Knauer, 1971; Brouillard and Barrett, 1973) but deaths from hepatic necrosis have occurred (Hoyumpa and Connell, 1973; Rehman *et al.*, 1973). Much interest has been aroused by reports of active chronic hepatitis developing in patients on methyldopa (Goldstein *et al.*, 1973). Many of the early descriptions of methyldopa hepatotoxicity dealt with single case reports or small groups of patients. We present here a series of 20 patients in whom liver damage appeared to be related directly to this drug.

Patients

The clinical features and laboratory data are shown in the table. Six patients had been seen in hospitals in the Nottingham and

Derby area in the previous three years (cases 6, 14, 15, 17, 18, and 20). The other 14 cases were originally reported to the Committee on Safety of Medicines, who sought permission from the reporting doctors before referring them to us so that further inquiries could be made. There were 14 women and six men in the series with an age range of 35 to 84 years. None admitted contact with infectious hepatitis and none of 11 patients tested were positive for Australia antigen or antibody. Two patients were taking another potentially hepatotoxic drug (chlorthalidone) at the onset of jaundice. In one of these patients chlorthalidone was restarted after her episode of liver damage without ill effects.

Drugs taken by other patients in addition to methyldopa included bendroflumazide, hydrochlorothiazide, frusemide, and chlorthalidone; amylobarbitone and nitrazepam; and nalidixic acid and thyroxine. So far as could be determined none of the patients were alcoholics or drug addicts.

Duration of Therapy

The duration of treatment and the total cumulative dosage of methyldopa are shown in fig. 1. Most of the patients became jaundiced between three and 16 weeks after beginning treatment. Four patients had recurrences of jaundice on second exposure to methyldopa. In two of these (cases 11 and 12) the second bout of jaundice reappeared promptly within two weeks of restarting the drug. None of the patients received unusually high daily dosages of methyldopa, the largest cumulative dosage being 448 g (case 15). One patient (case 13) died from fulminant hepatic failure four weeks after starting a second course of methyldopa. Five years earlier she had received this drug for eight weeks without developing jaundice, treatment having been stopped because of depressive symptoms.

Clinical Features

HEPATITIC SYNDROMES

Most patients had hepatitis-like reactions after taking methyldopa (cases 1-5, 7, 8, 11, 12, 14, 16, 17, 19, and 20). The symptoms were indistinguishable from those of viral hepatitis, with a prodromal period of anorexia, malaise, and fever followed by frank jaundice a few days later. Diarrhoea was a common early symptom. In these patients splenomegaly was not

General Hospital, Nottingham NG1 6HA

P. J. TOGHILL, M.D., F.R.C.P.ED., Consultant Physician
P. G. SMITH, M.B., M.R.C.PATH., Consultant Pathologist
PATRICIA BENTON, M.B., CH.B., Clinical Assistant
R. C. BROWN, M.B., M.R.C.P., Medical Registrar

Derbyshire Royal Infirmary, Derby

H. L. MATTHEWS, M.D., F.R.C.P., Consultant Physician

Clinical and Laboratory Data on Patients studied

Case No.	Sex	Age at Onset of Jaundice (years)	Maximum Total Serum Bilirubin (mg/100 ml)	Maximum Enzyme Levels (IU)		Maximum Alkaline Phosphatase		Histological Findings	Outcome
				SGPT	SGOT	K.A. units	IU		
1	M.	52	31.0	30		16.0		Hepatitis	Exploratory laparotomy. Recovered
2	F.	52	12.2		180	16.7			
3	F.	35	13.5	300		23.0			
4	F.	64	14.6	260		19.0			
5	F.	59	7.0	140		21.0			
6	M.	84	13.6	320	15	24.5	49.0		
								(1) Cholestatic hepatitis. (2) Normal liver at necropsy	Exploratory laparotomy. Recovered Died 12 months later from heart failure
7	M.	61	11.3	100		14.0		Chronic aggressive hepatitis	Recovered
8	F.	49	9.3	146		21.0			
9	F.	61	3.0	240		13.5			
10	F.	75	7.5	78		53.8			
11	F.	57	9.0		Not measured				
					430	17.2			
12	F.	60	5.4		700		61	Massive necrosis at necropsy Hepatitis (1) Severe hepatitis. Submassive necrosis. (2) Postnecrotic cirrhosis	Recovered Recurrence of jaundice after 2nd exposure. Recovered Recurrence of jaundice after 2nd exposure. Recovered Died. Fulminant hepatic failure Recovered
13	F.	68	25.4	140	200	15.9			
14	F.	36	2.9	287			76		
15	M.	51	18.7	86			124		
16	M.	62	6.3		940	29.0			
17	F.	37	11.5	275	Not measured	15.0			
18	F.	63	6.1	108			140	Macronodular cirrhosis at necropsy Hepatitis (1) Hepatitis. (2) Normal liver at necropsy	Died. Enormous retroperitoneal bleed Recovered Recovered from jaundice but died from uraemia after 10 months
19	F.	74	31.5	150	660	20.4			
20	M.	45	22.0	320			530

FIG. 1—Details of dosage of methyldopa.

*Second exposure to methyldopa.
†Uncertain—several weeks.

recorded, nor were there rashes, lymphadenopathy, or arthropathy. Jaundice cleared within three weeks of stopping methyldopa except in case 20, in which it persisted for two months. Liver function values were mainly in keeping with parenchymal damage, with high aminotransferase levels and normal or mildly raised alkaline phosphatase levels. The haematological findings were normal and there was no evidence of eosinophilia. In case 7 L.E. cells were detected during the acute phase of the illness though the clinical and biochemical features did not point to an active chronic hepatitis; liver biopsy was not performed.

Two patients (cases 6 and 10) presented with clinical and biochemical evidence of cholestasis. The history of one of these (case 6) is given below.

The patient, an 84-year-old man, was seen originally with jaundice, pruritus, and shivering attacks thought to be due to cholangitis. His total serum bilirubin was 13.6 mg/100 ml, serum alkaline phosphatase 49 K.A. units, and serum aspartate aminotransferase (SGOT) 15 IU. Coombs test gave a positive result and there was slight evidence of haemolysis. He had been taking methyldopa for three months but had stopped this drug just before admission to hospital. At laparotomy he had a firm liver and a normal pancreas. Operative cholangiography showed no large duct obstruction and a wedge biopsy specimen was taken. This showed features of a cholestatic hepatitis. The jaundice cleared

within two weeks of the operation and he made an immediate satisfactory recovery. After his death from heart failure a year later necropsy showed no hepatic disease apart from that related to the primary cause of death.

DOUBLE EXPOSURE

In four patients with hepatic syndromes (cases 4, 11, 12, and 17) there were recurrences of jaundice after second administrations of methyldopa. None of these were deliberate therapeutic challenges as methyldopa had not been incriminated positively as a cause for the jaundice in the first instance. Though in cases 11 and 12 there was a brisk recurrence of jaundice within two weeks of restarting methyldopa the course of the illness was similar and there were no clinical features of hypersensitivity.

SYNDROMES RESEMBLING ACTIVE CHRONIC HEPATITIS

In cases 15 and 9 respectively there were clinical and histological features of active chronic hepatitis.

Case 15.—This patient had been receiving methyldopa for 38 weeks for benign essential hypertension when he presented with a six-week history of jaundice, anorexia, and malaise. Examination showed an ill man with hepatomegaly, multiple spider naevi, and liver palms. Liver function tests showed total serum bilirubin 18.7 mg/100 ml, serum alkaline phosphatase 124 IU, serum alanine aminotransferase (SGPT) 86 IU, and total serum proteins 7.6 g/100 ml (albumin 2.5 g, globulin 5.1 g). Coombs test gave a positive result but there was no evidence of haemolysis. L.E. cells were present in large numbers. An immunofluorescent screen for autoantibodies showed antinuclear antibodies to be present in a titre of 1/40 but smooth muscle antibodies were absent. Liver biopsy showed changes of severe hepatitis with areas of submassive necrosis. Methyldopa was withdrawn and the patient slowly improved, losing his jaundice over the next two months. His serum albumin slowly increased to normal levels during the following year. Repeat biopsy five months after the onset of jaundice showed an inactive postnecrotic cirrhosis. When reviewed three and a half years after his original illness he was in excellent health and there were no abnormal physical signs apart from mild hypertension for which he was receiving debrisoquine. He declined further biopsy.

Case 9.—This patient, who had an uncomplicated clinical course suggestive of simple hepatitis, showed typical changes of chronic aggressive hepatitis on liver biopsy.

DEATHS FROM LIVER FAILURE

Case 18 showed the effects of methyldopa hepatotoxicity in a patient with clinically inapparent liver disease.

The patient was started on methyldopa because of benign essential hypertension. Three weeks later she was admitted to the surgical wards with jaundice; the significance of the methyldopa therapy was not appreciated. On admission her total serum bilirubin was 6.1 mg/100 ml, serum alkaline phosphatase 140 IU, and SGPT 108 IU. Two days later she suddenly collapsed with abdominal pain and died within minutes. A coroner's necropsy showed an enormous spontaneous retroperitoneal haemorrhage. The liver showed a macronodular cirrhosis but weighed only 660 g; histological examination, complicated by autolysis, confirmed the cirrhosis and in addition showed features consistent with hepatic cell necrosis.

In case 13 the patient died from fulminant hepatic failure seven weeks after starting a second course of methyldopa. At necropsy the liver was found to be small and shrunken, weighing 540 g.

HISTOLOGICAL CHANGES

Biopsy and necropsy specimens of liver were available from 10 patients; further histological evidence was obtained in four cases. Many common features were shared by the samples but three main patterns emerged. These were hepatitis, chronic aggressive hepatitis, and massive necrosis.

Cases 6, 14, 17, 19, and 20 showed predominantly hepatic features. Expanded portal tracts infiltrated by neutrophils, lymphocytes, and mononuclear cells with varying degrees of periportal inflammation dominated the picture (fig. 2). All samples except that from case 6 also contained eosinophils. There was a mild degree of bile duct proliferation. In addition there was evidence of focal and centrilobular necrosis and occasional Councilman bodies were present. All the samples showed evidence of regeneration with double liver cell plates. In case 6 there was severe cholestasis with bile plugs and moderate fatty change in liver cells. This patient died from heart failure a year later and at necropsy the liver showed an essentially normal pattern.

In case 15, in which the clinical syndrome suggested active chronic hepatitis, there were confluent areas of lobular collapse with condensation of reticulin and an intense inflammatory cell

infiltrate which contained plasma cells. Many liver cells showed ballooning degeneration, and plentiful Councilman bodies were present. Five months after stopping methyldopa repeat biopsy showed an inactive postnecrotic cirrhosis.

The typical histological features of chronic aggressive hepatitis were seen in case 9, in which there was distortion of the lobular pattern with irregular septa extending from portal tracts into the surrounding parenchyma which in some areas bridged across to centrilobular zones and adjacent portal tracts (fig. 3). In addition plasma cells were present in the inflammatory cell infiltrate.

At necropsy in case 13 the liver, which weighed 540 g, showed massive necrosis with isolated islands of surviving parenchyma, indicating attempted regeneration with nodule formation (fig. 4).

Discussion

These findings show that methyldopa is undoubtedly hepatotoxic. The strong temporal relation between administration of the drug and the development of jaundice supports this, but in four patients the ultimate proof was the reappearance of liver damage after second exposure. We accept that at times it is impossible to exclude a coincidental viral hepatitis even when histological material is available.

The precise nature of the hepatic reaction to methyldopa remains obscure and the results of this series point to a wide spectrum of response both clinically and histologically. Previous workers have commented on abnormal liver function values found during the first few weeks of methyldopa therapy (Irvine *et al.*, 1962; Sheps *et al.*, 1963; Colwill *et al.*, 1964) and in some cases these abnormalities have reverted to normal without stopping treatment (Leonard *et al.*, 1965; Smith *et al.*, 1966). Most of these reports have described patients with hepatic reactions without diagnostic histological features in the liver (Elkington *et al.*, 1969; Tysell and Knauer, 1971). From our experience in this series the mixed inflammatory cell portal infiltrate and the presence of eosinophils may help to distinguish methyldopa liver damage from viral hepatitis. The two patients in our series with predominantly cholestatic hepatitis were unusual and we are unaware of any previous similar accounts.

There have been other reports of histological features of chronic aggressive hepatitis in patients taking methyldopa.

FIG. 2—Case 14. Needle biopsy specimen of portal tract showing hepatic reaction. (H. and E. $\times 126$.) FIG. 3—Case 9. Needle biopsy specimen of portal area showing chronic aggressive hepatitis. (Reticulin stain. $\times 82$.) FIG. 4—Case 13. Necropsy specimen of liver showing massive necrosis. (H. and E. $\times 125$.)

Williams and Khan (1967) were the first to draw attention to this in one of their patients, and confirmation has come from Hoyumpa and Connell (1973) and Goldstein *et al.* (1973). The latter authors, in an investigation of the aetiology of 21 consecutive cases of active chronic hepatitis in their unit in 12 months, found no fewer than 14 cases which they considered to be drug induced. Of these, nine were associated with ingestion of oxyphenisatin and five methyl dopa. In an analysis of the histological features they found that in active chronic hepatitis due to methyl dopa there was milder liver cell necrosis and a lower incidence of cirrhosis than in active chronic hepatitis due to oxyphenisatin and active chronic hepatitis of unknown origin. They also commented on the better initial improvement in patients with chronic hepatitis who were able to stop taking their drug as compared with those in the "unknown origin" group. As with the haemolytic anaemia due to methyl dopa it seems likely that the development of active chronic hepatitis has an immunological basis. Unfortunately autoantibody studies were not always reported in earlier papers and, in particular, the incidence of smooth muscle antibody is not known.

While proof of the aetiological role of methyl dopa may be obtained by a rechallenge with the drug we feel that this is a highly dangerous procedure which may be followed by fatal hepatic necrosis. Some of the deaths from hepatic necrosis reported in the literature have resulted from accidental or deliberate rechallenge with the drug (Rehman *et al.*, 1973; Hoyumpa and Connell, 1973). Though the first episode of liver damage may be delayed for several weeks after the initial treatment with methyl dopa it seems clear that readministration of the drug may elicit a prompt and dramatic exacerbation of the liver injury.

In view of the high incidence of mild abnormalities in liver function after starting treatment with methyl dopa we feel that there is little point in carrying out routine tests during the first few weeks of treatment. Clearly routine testing will not screen out those patients who may progress to clinical liver damage. Our experience, however, of a patient with undiagnosed cirrhosis who died from superimposed liver damage from methyl dopa indicates the need for caution. It seems prudent, therefore, to check the results of routine liver function tests

before starting treatment in all patients, and it is clearly dangerous to give methyl dopa to patients with overt liver disease. An awareness of the possibility of methyl dopa hepatotoxicity is probably the most important point and, above all, there must be a strict avoidance of the temptation to perform a clinical rechallenge, an exercise which may result in disaster.

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Essential Thrombocythaemia and Peripheral Gangrene

F. E. PRESTON, I. G. EMMANUEL, D. A. WINFIELD, R. G. MALIA

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Summary

Six patients are described in whom gangrene of one or more toes occurred as the presenting feature of essential thrombocythaemia. Spontaneous platelet aggregation was observed in platelet-rich plasma from four patients and platelet aggregation after the addition of adenosine diphosphate and

collagen was highly abnormal in samples from all six. All of the patients described dramatic relief of pain within six hours of ingestion of aspirin and this coincided with disappearance of the spontaneous platelet aggregation and collagen-induced platelet aggregation. Treatment with phosphorus-32 corrected the platelet count and there were no further recurrences of peripheral vascular disease. Platelet function tests performed at the time all gave normal results. It is concluded that essential thrombocythaemia is an important and treatable cause of peripheral vascular disease.

University Department of Haematology, Royal Infirmary, Sheffield S3 3DA

F. E. PRESTON, M.D., M.R.C.PATH., Consultant/Associate Haematologist
 D. A. WINFIELD, M.R.C.PATH., Senior Registrar
 R. G. MALIA, F.I.M.L.T., Senior Chief Technician

Weston Park Hospital, Sheffield S10 2SJ

I. G. EMMANUEL, F.F.R., Consultant Radiotherapist

Introduction

Though vascular thromboses are a known complication of essential thrombocythaemia it is usually major vessels which are affected (Gunz, 1960) and there have been surprisingly few reports on the importance of this condition as a cause of peripheral vascular disease.