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LIVER FUNCTION PROFILE IN PATIENTS TAKING METHYLDOPA

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Abstract

Liver function tests were done in 100 patients who had taken methyldopa for a variable period and 96 hypertensives taking other anti-hypertensive agents who served as controls. The groups were approximately comparable in regard to the intake of other drugs. The frequency of abnormal SGPT and SGOT values was higher in the methyldopa group (27-32%) as compared with the controls (11%). Of those showing abnormal transaminases values amongst the methyldopa group, the rise was mild (<70 i.u.), in nearly three fourth with a general tendency to revert to normal levels inspite of continued drug administration. In a small group the transaminases values tended to deteriorate. A small prospective study also showed a mild rise of transaminases in a significant number following administration of methyldopa. No evidence of clinical liver disease or overt hepatotoxicity possibly related to drug was observed. Methyldopa remains a useful drug but should be avoided in those with evidence of liver disease. The study also highlights the importance of drug history in the interpretation of liver function tests.

Introduction

Methyldopa is a potent anti-hypertensive agent and is widely used in clinical practice. The drug is generally well tolerated and is free from serious side effects. On rare occasions liver dysfunction has occurred following its use (Gillespie 1960; Elkington et al., 1969; Irvine et al., 1962). Most reports have described a picture simulating hepatitis which is reversible on withdrawal of the drug (Elkington te al., 1969; Tysell and Knauer, 1971; Cannon and Laragh, 1963), but on rare occasions deaths from hepatic damage have also occurred (Hoyumpa and Connell, 1973; Rehman et al., 1973). The other rare hepatic syndromes associated with methyldopa include chronic active hepatitis (Goldstein et al., 1973), granulomatous hepatitis (Miller and Reid, 1976) and cholestatic jaundice (Hoffbrand et al., 1974).

In this country some studies have documented liver dysfunction in a small but sizeable percentage of apparently normal subjects (Ahmad and Quraishi, 1975; Haider et al., 1975). In view of the widespread use of methyldopa in clinical practice and its propensity to cause hepatic dysfunction in some, we studied the liver function profile in hypertensive patients taking methyldopa.

Material and Methods

In the first part of the study, liver function profile was studied in 100 hypertensives attending the Hypertension Clinic of PMRC Unit at Lahore. These patients had been taking methyldopa for a variable period ranging between 6 months to 1-1/2 year. For the sake of comparison 96 hypertensives, who were taking drugs other than methyldopa were also investigated. A detailed drug history was taken on each visit to document the intake of any other potentially hepatotoxic drug. In all patients, special attention was paid to inquire about past history of liver disease as well as any prodromal symptoms of impending liver damage such as fever, rash, abdominal pain, malaise and discoloration of urine etc.

In the second part of the study, which was designed to be prospective, liver function profile was studied in 25 patients before starting methyldopa. The tests were repeated in 14 patients after they had taken methyldopa for a period ranging between 3-12 months.

The serum transaminases were expressed as Karman units, (normal: SGOT 8-40 units; SGPT 5-35 units) and alkaline phosphatase as K.A. units (normal 3-13 units). The other biochemical investigations which included serum bilirubin, serum protein, albumin: globulin ratio were done according to methods described by King and Wooten (1964).

Results

A. Random Study (Table I):

The abnormality in transaminases was

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arbitrarily divided into mild (≤70 units) and significant (770 units). Of the 100 patients taking methyldopa elevations of SGOT and SGPT were found in 32 and 27 patients respectively. Twenty four of these patients had only mild elevation of transaminases and in these the frequency of relevant clinical features included diabetes mellitus (2), past history of cholecystitis (2), history of jaundice (1) and mild hepatomegaly (2). 8 patients in the methyldopa group had a significant elevation of SGOT with similar elevation of SGPT in 3 of them. All these 8 patients also had elevation of alkaline phosphatase. The frequency of relevant clinical features included diabetes mellitus (2), and a history of jaundice and hepatomegaly in one patient in whom liver biopsy showed chronic active hepatitis.

In the 96 patients comprising the control group, elevation of transaminases values were declared in 11 (11.4%), with associated abnormality in alkaline phosphatase in 4(4.16%). In the methyldopa group, further follow up observations were made in 23 patients with abnormal transaminases (6 with significant elevation and 17 with mild elevation). All 6 patients with significant abnormality showed further deterioration. In 2 of these patients transaminases were repeated 3 months following withdrawal of methyldopa but no significant improvement was noted. Of the 17 cases with mild rise of transaminases, liver functions reverted to normal in 12 inspite of continued intake of drug. In the other 5 mild deterioration in transaminase values was observed.

B. Prospective Study (Table II)

24 patients had liver function tests done before starting methyldopa. In these, mild elevation of SGOT and SGPT were noted in 2(8.3%) and 3(12.5%) respectively. Alkaline phosphatase values were abnormal in 4(16.6%) patients.

Table I: Liver Function Tests in Hypertensive Patients: Methyldopa and Control Groups.

L.F.T.	*MYTHYLDOPA GROUP*				*CONTROL*			
	Total No. of patients tested	*Abnormal tests (No. of patients)*	*Percentage with abnormal value*	*Range of abnormality*	*Total No. of patients tested*	*Abnormal tests (No. of patients)*	*Percentage with abnormal value*	*Range of abnormality*
SGOT	100	32	32	46-170 i.u.	96	11	11.45	45-84 i.u.
SGPT	100	27	27	44-124 i.u.	96	11	11.45	44-130 i.u.
Alkaline phosphatase (K.A. unit)	100	8	8	16-25.2	96	4	4.17	15.6-24.8
Serum bilirubin (mg%)	100	—	—	—	96	—	—	—
A/G ratio	100	2	2	0.5-0.6	96	3	3.12	0.7

Table II: L.F.T. Before and After Taking Methyldopa in Hypertensive Patients.

L.F.T.	*MYTHYLDOPA GROUP*				*CONTROL*			
	Total No. of patients tested	*Abnormal tests (No. of patients*	*Percentage with abnormale value*	*Range of abnormality*	*Total No. of patients tested*	*Abnormal tests (No. of patients*	*Percentage with abnormal value*	*Range of abnormality*
	BEFORE METHYLDOPA				*AFTER METHYLDOPA*			
SGOT	24	2	8.3	40-46 i.u.	14	7	50	45-70 i.u.
SGPT	24	3	12.5	40-50 i.u.	14	6	42.85	40-70 i.u.
Alkaline phosphatase (K.A. units)	24	4	16.6	16-18	14	—	—	—
Serum bilirubin (mg%)	24	—	—	—	14	—	—	—
A/G ratio	24	1	4.17	0.7	14	—	—	—

Table III: Drug History in Methyldopa and Control Groups

Drug History	*Methyldopa group (100 patients)*	*Control Group (96 patients)*
I. Diuretics:		
1. Thiazides	37	46
2. Frusemide	36	1
3. Spironolactone	1	—
II. Anti-hypertensive Agents:		
1. Reserpine	20	14
2. Guanethidine	9	2
3. Adelphane	4	4
4. Proprenolol	4	2
5. Bethenidine	1	—
III. Sedatives and Tranquillizers (e.g. Diazepam, Lorazepam, Phenobarbitone etc.)	23	25
IV. Anti-diabetic Agents:		
1. Oral anti-diabetics (Chlorpropamide, Glibenclamide and Metformin etc.)	21	24
2. Insulin	2	1
V. Misc. Drugs:		
1. Digoxin	3	1
2. Dindevan	1	1
3. Gylceral Trinitrate	2	—
4. Aminophylline	2	1
5. Hasheesh	—	1

Liver function tests were repeated in 14 patients after 6-18 months of therapy. Mild elevation of SGOT and SGPT were recorded in 7(50%) and 6(42.8%) patients respectively. There were no apparent relationship between liver function tests abnormality and dose of the drug.

In view of the possibility of intake of other drugs which could cause liver dysfunction, a thorough drug history was taken which showed that there was no apparent difference between the control and methyldopa groups (Table III). The potentially hepatotoxic drugs taken by patients included anti-diabetics and sedatives which were distributed equally in both the control and methyldopa groups.

Discussion

A study such as this presents difficulty in that it is not always possible to separate the effects of other drugs being ingested by the patients. However, a thorough search of the drug history in the methyldopa and control groups revealed that the groups were reasonably balanced, particularly in respect to the relative frequency of intake of anti-diabetic and sedative drugs.

The incidence of serum transaminases abnormalities was nearly 30% in the methyldopa group as compared with the 11% in the control. This elevation of transaminases in the methyldopa group was mild in three fourth of the patients and tended to improve in most inspite of continued therapy with methyldopa. This phenomenon is not unknown and has been observed by others (Weil et al., 1963; Sheps et al., 1963). In those with a significant elevation of transaminases values, there was tendency for their values to deteriorate further with continued administration of drug, but without any clinical evidence of overt hepatotoxicity. Chronic active hepatitis is another rare syndrome associated with methyldopa therapy (Goldstein et al. ,1973). In one of our patients with histological evidence of chronic active hepatitis, the role of drug was doubtful in view of a very probable attack of viral hepatitis 4 years earlier before exposure to the drug. The prospective study in a relatively small number of patients also confirmed mild rise of transaminases in a significant proportion following the introduction of methyldopa therapy.

The exact significance of mild disturbance in the transaminase values unassociated with overt evidence of liver disease remains obscure. The commonsense would dictate that methyldopa should be avoided in patients with obvious liver disease and a careful history is essential. The study highlights the fact that a drug induced rise in transaminases may cause difficulties in the interpretation of liver function tests and underscores the importance of drug history in such situations. It may be relevant to point out that other drugs such as isoniazid have also been shown to cause a reversible rise of transaminases values.

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