Hepatocellular damage due to Methyldopa

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METHYLDOPA HAS BEEN widely used as an antihypertensive agent because postural hypotension is considerably less frequent and less severe than during treatment with guanethiadine or a ganglion blocking agent. Toxic reactions associated with its use have not been common and these include granulocytopenia, drug fever and haemolytic jaundice. There have been frequent reports of the development of a positive Coomb's test without evidence of haemolysis in patients receiving the drug but this did not necessitate its withdrawal. The occurrence of jaundice due to liver damage in patients on methyldopa as a toxic manifestation is not widely recognised hence it is thought worthwhile documenting this case.

Case Report

The following is a case report of a patient who developed jaundice while receiving methyldopa. E.J. was a 24-year-old Indian woman, who was admitted on 24th December 1968, complaining of sudden onset of weakness of the right side of her face and inability to close her right eye. On examination, she was found to have a right lower motor neurone type of facial palsy and an elevated blood pressure of 170/120 mm.Hg. Her peripheral pulses were all felt and equal on both sides, and her heart was normal. Examination of other systems revealed no abnormalities. Investigations did not reveal any cause for her hypertension and as she had a strong family history, she was thought to have essential hypertension. Her blood pressure was satisfactorily controlled on reserpine 0.25 mg. t.d.s. and hydrochlorothiazide 25 mg. daily. About two months later, she was reviewed in the outpatient clinic and because of poor control of her blood pressure, methyldopa was substituted for reserpine. Six weeks later, she was readmitted because ofanorexia, vomiting and darkening of her urine for three days. She was afebrile and jaundiced but the liver and spleen were not palpable. The serum bilirubin was 4.9 mg/100 ml. of which 3.2 mg was conjugated; SGPT was 1240 I.U. and alkaline phosphatase was 18.5 K.A.U. Her serum proteins was 8.3 gm/100 ml with a normal albumin/globulin ratio. The urine contained a trace of bilirubin and urobilinogen. Methyldopa was stopped and she rapidly improved in that her symptoms subsided and a week after admission, her bilirubin fell to 3.7 mg/100 ml and the SGPT to 370 I.U. She was re-started on reserpine 0.25 mg b.d. and hydrochlorothiazide 25 mg daily. Her jaundice cleared completely after three weeks.

A week later, when seen in the outpatient clinic, she was again given methyldopa in addition to reserpine and hydrochlorothiazide to control the blood pressure at normotensive levels. After taking methyldopa for two weeks, she again developed symptoms of anorexia, vomiting, pruritus and jaundice. Two weeks after onset of jaundice, she returned to hospital. On examination, she was deeply jaundiced, the liver was tender and enlarged 3 cm below

the right costal margin, the spleen was just palpable and there were many scratch marks on the skin. The serum bilirubin was 10.6 mg/100 ml of which 4.1 mg was conjugated, SGPT 640 I.U. and the alkaline phosphatase level was 13.8 K.A.U. The urine contained bilirubin but no urobilinogen. The direct Coomb's test was negative and a plain X-ray film of the abdomen showed no opacities to suggest the pressure of gall stones. Twelve days after stopping methyldopa, the serum bilirubin fell to 4.5 mg/100 ml, the SGPT to 196 I.U. and the urine contained urobilinogen but no bilirubin. She made an excellent recovery and when seen in the clinic 10 weeks after discharge, she had no jaundice, the serum bilirubin was 0.6 mg/100 ml. SGPT was 31 I.U. and the alkaline phosphatase was 6.5 K.A.U.

Discussion

The Medical Letter (1) recently reviewed the adverse effects of drugs on the liver. The two principal types of adverse hepatic reactions recognised were cholestasis and viral hepatitis-like damage of the liver. It was thought that whereas cholestasis was not a hypersentivity reaction, the viral hepatitis-like injury to the liver was the result of a hypersensitivity reaction. Methyldopa was one of the drugs incriminated to produce the latter type of effect.

Williams and Khan (2) in 1967 reported on the occurrence of non-haemolytic jaundice in two patients receiving methyldopa for the treatment of hypertension. One patient had symptoms of malaise, nausea, anorexia associated with progressive jaundice and dark urine, similar to that of viral hepatitis. The other complained of epigastric discomfort and jaundice. The patients had been exposed to the drug for six weeks and seven months respectively. In both patients, the serum glutamic pyruvic transaminases were markedly elevated and these returned to normal 8 weeks in one patient and 10 weeks in the other, after methyldopa was withdrawn. Coomb's test was negative in the first patient but positive in the second who also had an elevated alkaline phosphatase.

Another report was by Wyburn-Mason and Anastassiades (3) who noted the occurrence of jaundice in a patient who had been treated with methyldopa for about six weeks. Four-and-a-half weeks after stopping the drug, the jaundice disappeared and the elevated SGPT returned to normal. Morin et al (4), in a clinical study of 28 hypertensive patients on methyldopa therapy for an average of 8 weeks, found one who developed a raised SGPT. This fell to normal after the drug was stopped. Four months later, when therapy was testarted, the SGPT level rose again, falling as before on withdrawal of the drug. Irvine (5) reported a transient rise in serum glutamic oxalo-acetic transaminase in 4 out of 15 patients receiving methyldopa for a mean period of 16 weeks. The level was reported to fall to normal without stopping treatment over this period, but the exact time interval was not specified.

In the case reported above, the appearance of jaundice and viral hepatitis-like symptoms, together with abnormal liver function tests occurring on two occasions following methyldopa therapy and the apid improvement clinically and biochemically when the drug was withdrawn, strongly suggest that the liver dysfunction was drug-induced.

If a patient receiving methyldopa develops jaundice, drug sensitivity must be thought of as a cause because the toxic effect on the liver appears to be reversible. All recorded cases and the one reported here have made a rapid complete recovery on withdrawal of the drug (7).

References:–

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7. Council on Drugs (1963) *American Medical Association Journal* 186. 505.