Brit. J. Psychiat. (1967), 113, 1113–1114

Intrahepatic Obstructive Jaundice from Amitriptyline

By R. W. BIAGI and B. N. BAPAT

The past decade has seen many new drugs. With use, serious side-effects have become apparent. The need for rapid assessment and advertisement of such effects led to the formation of the 'Dunlop Committee'.

We wish to report here presumptive evidence of amitriptyline (Tryptizol) causing jaundice from intrahepatic bile retention, which we believe has not so far been reported.

Jaundice of two types may be caused by the anti-depressant drugs. The hydrazide division of monoamine oxidase inhibitors produces hepatocellular jaundice; imipramine (Tofranil) produces intrahepatic bile retention resembling in every respect that produced by the phenothiazines. No serious liver dysfunction was noted as resulting from the use of amitriptyline until acute hepatic necrosis was reported with amitriptyline, and also with diazepam (Valium), by Cunningham in 1965. Reference has been made to changes in transaminase levels (Holmberg and Jansson, 1962) in the blood of patients under treatment with amitriptyline, but no reference to intrahepatic bile retention has been so far discovered by us in the literature.

Case History

Mrs. M.J. came under our care in 1964 with a right basal pneumonitis and pleural effusion. With treatment this cleared and was accepted as a non-specific infective episode. She remained well until March 1966, when she began complaining of frequency of stools, without blood or mucus. Investigations, including a barium enema, gave normal results, and she improved with symptomatic treatment. She remained well until June 1966, when she suddenly complained of severe pain in the epigastrium and right hypochondrium. The pain did not radiate to the back and was not associated with nausea or vomiting; it disappeared within two hours and did not recur, but 24 hours later there was clinical evidence of jaundice associated with itching. There was no history of previous dyspepsia or intolerance to fatty foods, nor was there any associated diarrhoea or pyrexia.

In December 1965 she had complained of swelling of her ankles, and her doctor had put her on Lasix 20 mg. twice a week, on which regimen she had remained. At the end of November 1965, because of depression, he had prescribed amitriptyline in the form of Tryptizol syrup (10 mg. amitriptyline base three times a day) and this was continued for two months with marked improvement. Three weeks before the onset of jaundice she had again become depressed, and amitriptyline had again been prescribed and was continued until the jaundice appeared.

Clinical examination during the pain and following the appearance of jaundice did not reveal any abnormality in the abdomen or chest, nor any evidence of heart failure.

Stools were putty coloured. Hb. was 94 per cent. and W.B.C.s 8,000 per c.mm. with polymorphs 70 per cent. and lymphocytes 30 per cent. Straight X-ray of abdomen showed no gallstones nor any other abnormality. Urine contained bile salts, urobilin and urobilinogen.

S.G.O.T. was 32 units; S.G.P.T. 14 units and L.D.H. 375 units. Plasma proteins were 6·2 grams per cent., albumen being 4·4 grams per cent. and globulin 1·8 grams per cent. Electrophoretic pattern was normal. Serum electrolytes were normal. Blood urea was 31 mg. per cent. E.S.R. was normal throughout.

Chest X-ray showed no abnormality. A barium series was performed and no abnormality was found.

Liver function tests were as follows:

Day	8th	16th	21st	23rd	29th	37th
Serum bilirubin (mg. per cent.)	3·8	8·7	12	11	10	9
Alkaline phosphatase (K.A. units)	27·3	29·3				
Thymol turbidity	1	1				
Thymol flocculation	Neg.	Neg.				
Serum colloidal gold	Neg.	Neg.				

As the patient continued to be jaundiced, exploratory laparotomy was carried out on the 29th day. The liver was slatey in colour and slightly enlarged. The common bile duct was green and normal, and no abnormality was found in the abdomen. No hepatic lesion was demonstrated by cholangiogram. Biopsy was taken from the anterior aspect of the liver.

The pathologist reported: "The appearances are indicative of obstructive jaundice, i.e. distension of bile canaliculi with bile and retention of bile in liver cells, both features being most marked in the centre of the liver lobules. Besides blockage due to mechanical causes outside the liver, these appearances are found in cases of jaundice arising after chlorpromazine therapy."

Thereafter there was steady progress, and four weeks later serum bilirubin was 1·3 mg. per cent.

https://doi.org/10.1192/bjp.113.503.1113 Published online by Cambridge University Press

Comment

Examination at laparatomy and cholangiography exclude any possibility of the jaundice being caused by an extrahepatic obstruction. The histological picture excludes an infective hepatitis.

The following points are in favour of the jaundice being drug-induced.

(1) Drugs which can be implicated are Lasix and amitriptyline. Lasix has not been known to cause liver dysfunction, but the tricyclic dibenzepine derivatives such as amitriptyline show some chemical similarity to chlorpromazine which is known to produce cholestatic jaundice. Liver necrosis has been reported as probably resulting from this drug

(2) 80 to 90 per cent. of cases of chlorpromazine-induced jaundice occur within the first month of treatment (Sherlock, 1963). Here, jaundice occurred in the third week of the second course.

(3) The clinical picture is compatible, e.g. the prodromal abdominal pain (Sherlock) and the severe itching of the skin at an early stage. The presence of urinary urobilinogen throughout the illness is against an infective hepatitis; the absence of prodromal anorexia and the moderate degree of anorexia throughout favour drug-induced jaundice; the levels of serum bilirubin and alkaline phosphatase and the negative sero-flocculation tests also favour a drug-induced origin.

(4) The histological picture of the liver biopsy is strikingly in favour.

Altogether four types of drug jaundice have been described: (1) Haemolytic jaundice; (2) Intrahepatic cholestasis due to hypersensitivity; (3) A non-sensitive type of intrahepatic cholestasis; (4) Hepato-cellular jaundice.

The findings here are those of an intrahepatic cholestatic jaundice, identical to that known to be caused by chlorpromazine and suggestive of the hypersensitive type.

Summary

A case is described of jaundice due to intrahepatic bile retention in which the patient had been taking amitriptyline in therapeutic doses. This has not been reported hitherto.

References

Cunningham, M. L. (1965). "Acute hepatic necrosis following treatment with amitriptyline and diazepam." *Brit. J. Psychiat.*, **111**, 1107–1109.

Holmberg, M. B., and Jansson, B. (1962). "Study of blood count and serum transaminase in prolonged treatment with amitriptyline." *J. new Drugs*, **2**, 361–365.

Sherlock, S. (1963). *Diseases of the Liver and Biliary System.* (3rd edition). Oxford: Blackwell. p. 392.

R. W. Biagi, M.B.E., M.B., Ch.B., M.R.C.P.E., *Physician Superintendent*

B. N. Bapat, M.B., B.S., D.T.C.D., *Senior Hospital Medical Officer*

Llangwyfan Hospital, Denbigh, North Wales

(*Received 20 September, 1966*)

https://doi.org/10.1192/bjp.113.503.1113 Published online by Cambridge University Press