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Jaundice Associated with Amitriptyline

By D. H. MORGAN

Reports of serious complications arising from the administration of amitriptyline have been very few, particularly when account is taken of the widespread prescription of this drug in recent years for depressive illness. This is a report of three cases of jaundice, one mild, one fatal, and the third severe, but leading to a good recovery, occurring following the administration of amitriptyline, though in two cases other drugs were being given concurrently. The makers of amitriptyline do include in their literature a caution about the very occasional link with jaundice, but only two cases have so far been reported (Cunningham, 1965; Biagi and Bapat, 1967). In a recent article (Sherlock, 1968), no specific mention was made of amitriptyline in particular, or of tricyclic antidepressant drugs in general, as liable to produce hepatic disorder.

Case 1

This 40-year-old man became depressed in August, 1964. Treated by his G.P. with nortriptyline 75 mg. t.d.s., he failed to improve. On 7 September, 1964, he was started on amitriptyline 25 mg. q.d.s., and Tuinal 200 mg. nocte: on 17 November, 1964 chlordiazepoxide 10 mg. t.d.s. was added.

On 20 December, 1964, jaundice slowly appeared, preceded by abdominal discomfort for a few hours and pale loose stools for two days. No fever was noted, but he had some nausea and vomiting. There was no history of contact with viral hepatitis, and he had had no injections over the preceding six months.

A week later the colour returned to his stools, but he remained jaundiced and developed a generalized itchy maculo-papular rash. He continued on these drugs until his admission to hospital on 15 January, 1965. At this time his serum bilirubin was 42 mg./100 ml.; S.G.O.T. 2,050 units; S.G.P.T. 1,600; and alkaline phosphatase 27·0. There was no quick response to treatment with prednisolone, but the jaundice slowly subsided so that on 3 March, 1965, he went home with serum bilirubin 2·7 mg./100 ml.; S.G.O.T. 110 units; S.G.P.T. 96 units; and alkaline phosphatase 16·0. He was taking glutethimide 200 mg. nocte, changing to Tuinal 200 mg. nocte on 14 April, 1965.

On 15 May, 1965, he developed headaches, became more jaundiced and was readmitted. A liver biopsy showed a severe diffuse cellular reaction with some patchy necrosis and parenchymal fibrosis. His condition deteriorated, not responding to prednisone, streptomycin and neomycin, so that he was in semi-coma. On 31 July, 1965, he was operated on for a perforated duodenal ulcer, but his general condition worsened and he died on 6 August, 1965.

At post mortem, the liver (weight 1,840 gm.) was firm, with preservation of the lobular architecture and fibrosis of the portal tracts, with an infiltration by lymphocytes and plasma cells. There was marked proliferation of bile ductules, and large plugs of bile pigment in the canaliculi. No evidence of liver cell necrosis.

Case 2

Late in 1964, this 45-year-old man developed a depressive illness with hypochondriacal features. Full medical examination revealed no abnormal findings. On 25 March, 1965, he was prescribed amitriptyline 25 mg. t.d.s., increasing to 50 mg. t.d.s. on 30 March, 1965. His depression improved.

On 18 April, 1965, he felt sick and vomited several times; his urine became dark, his stools pale. He was admitted to hospital on 26 April, 1965, still vomiting, mildly jaundiced, but apyrexial. His drugs were stopped on 28 April, 1965. Investigations were as follows: WBC 3,300; ESR 3 mm.; serum bilirubin 1·6; S.G.O.T. 50 units; S.G.P.T. 40 units; alkaline phosphatase 9·6.

He improved swiftly, his jaundice cleared and he has remained well. There was no history of contact with viral hepatitis, he had received no injections, and all blood samples taken during his earlier medical check were done with disposable syringes and needles.

Case 3

This woman, aged 24, was first treated by her G.P. with meprobamate and Tuinal for a depressive illness. On 5 April, 1966, amitriptyline 25 mg. t.d.s. was started, increasing to 50 mg. t.d.s. on 12 April, 1966. She also took Tuinal 200 mg. nocte. On 20 June, 1966, she felt tired, developed nausea, so went to her G.P. who added chlordiazepoxide 10 mg. t.d.s. On 27 June, 1966, she was obviously jaundiced, her urine dark, stools pale and loose. All drugs were stopped on 2 July, 1966. On 13 July, 1966, tests were as follows: serum bilirubin 13·2 mg.; S.G.O.T. 1,140 units; S.G.P.T. 800 units; alkaline phosphatase 15·6 units. She also developed considerable oedema of the legs and abdomen, but this cleared after she miscarried on 20 August, 1966. The jaundice settled by mid-September, but her mood was very unpredictable. On 11 November, 1966, she took an overdose of chlordiazepoxide 40 mg. and Tuinal 400 mg., but was none the worse for it. Her S.G.O.T. was 46 units; S.G.P.T. 26 units.

On 21 November, 1966, she took an overdose of amitriptyline 75 mg. and Tuinal 400 mg.; she recovered

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from the immediate effects, but on 25 November, 1966, she became tired, lost her appetite, and passed loose stools, just as in June. The transaminase levels rose sharply to S.G.O.T. 190 units; S.G.P.T. 160 units, falling gradually to normal by January, 1967. Two further overdoses of chlordiazepoxide have not caused any symptoms, nor any rise in transaminase levels. Before the illness she had not been in contact with viral hepatitis, and two injections from her G.P. were given with disposable syringes.

Discussion

Over the past ten years there have been many reports of psychotropic drugs causing, or being associated with, jaundice. The causal link is often hard to prove since it is difficult to exclude viral or serum hepatitis as possible causes (H. Popper, 1958). Usually the clinical picture from hepatitis caused by a hypersensitivity reaction resembles acute viral hepatitis except for the absence of pre-icteric fever and constitutional symptoms (Hargreaves and Lathe, 1964). Anorexia, nausea and vomiting are the principal symptoms. The laboratory findings are akin to those in viral hepatitis though with less striking changes in flocculation and turbidity. In each of these cases the flocculation tests were negative.

The type of jaundice in each of these cases appears to be both hepatocellular and cholestatic, with a variable mixture of the two. All reports on drug-induced jaundice have noted that, although recovery is the rule and occurs fairly swiftly after the drug has been stopped, subacute hepatic necrosis can occur, and may lead on to cirrhosis and prove fatal, as in Case 1.

These three patients all developed jaundice after taking amitriptyline. Only in Case 2 was no other drug given. The other two patients were also given chlordiazepoxide, which has been reported as a cause of jaundice (Cacioppo and Merlis, 1961; Abbruzzese and Swanson, 1965; Pickering, 1966), so that it can be argued that either the amitriptyline, or the chlordiazepoxide, or the combination of these two drugs provoked the hepatitis. Yet the best evidence of a particular drug being responsible is to be found if the hepatitis recurs when the drug is exhibited a second time; and in Case 3 this happened when the patient had the temerity to take an overdose of amitriptyline, with a consequent worsening of her condition; on the other hand there was no upset when she took an overdose of chlordiazepoxide.

In these three cases the mildest hepatitis occurred when the drug was promptly stopped, the fatal case where it continued to be prescribed for some time. Without doubt any drugs being prescribed at the time of jaundice first appearing should be suspended until a careful appraisal is made of the nature of the jaundice and the likely toxicity of the drug or drugs.

Summary

Three cases of jaundice occurring during the administration of amitriptyline are reported. In two of the cases other drugs were also being given, but on the evidence, were less likely to be responsible for the hepatitis.

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