Hepatitis from dantrolene sodium

S. P. WILKINSON, B. PORTMANN, AND ROGER WILLIAMS

From the Liver Unit, King's College Hospital and Medical School, Denmark Hill, London

SUMMARY The clinical course and histological changes in the liver during a presumed adverse reaction to the drug dantrolene sodium are described in four patients. After a typical prodrome one developed a moderately severe hepatitis-like illness. Another also had a prodrome but never became jaundiced. In the other two, abnormal liver function tests were detected on routine screening. In each case liver biopsy showed changes typical of an acute hepatitis, but the severity was unrelated to the clinical presentation. In addition, there were also changes in the portal tracts resembling ascending cholangitis. In each case liver function tests returned to normal after withdrawing treatment with dantrolene.

Dantrolene sodium is a hydantoin/furan derivative used for the management of spasticity (Snyder *et al.*, 1967). Since its introduction to Great Britain in 1975, there have been reports from the USA of hepatic damage occurring during therapy (Ogburn *et al.*, 1976; Schneider and Mitchell, 1976; Utili *et al.*, 1977). In one study 19 (1.8%) of 1044 patients taking dantrolene sodium for more than 60 days developed abnormal liver function tests. Six became jaundiced, and three died, presumably as a result of the liver disease, although this was not specifically stated (Utili *et al.*, 1977). Sixteen of another 29 patients who had developed jaundice while receiving dantrolene also died (Utili *et al.*, 1977). The most common type of liver injury described is chronic active hepatitis, although acute hepatitis, cirrhosis, massive hepatic necrosis, and a non-specific portal infiltrate have also been reported.

In the present paper we report four cases which, on liver biopsy, showed histological features of both an acute hepatitis and an ascending cholangitis (cholangiolitic hepatitis).

Case reports

The four cases were referred to us either because of the development of jaundice or because of the finding of abnormal liver function tests on routine biochemical screening. All had normal liver function tests immediately before treatment. These had been subsequently checked at six weeks and three months unless they had already been referred. Cases 2 and 3 were not receiving any other medication. Case 1 was also receiving L-dopa and haloperidol, and case 4 the

anticholinergic drug emepromium bromide. The serum was negative for HBsAg and autoantibodies in all cases at the time of referral and throughout the course of the adverse reaction.

CASE 1

A 64 year old man with a longstanding familial tremor and rigidity, after taking dantrolene for one month (initially 25 mg/day increasing to 100 mg/day), developed lethargy, anorexia, and malaise. Dantrolene was discontinued, but the symptoms persisted and two weeks later he noticed jaundice with pale stools and dark urine. The serum bilirubin concentration rose to 320 $\mu\text{mol/l}$ (normal < 20), the aspartate aminotransferase (AST) to 550 IU/l (normal < 40), the alkaline phosphatase (AP) to 171 IU/l (normal < 80), and the prothrombin time became nine seconds prolonged (Table). He remained jaundiced for six weeks and during the subsequent six weeks the liver function tests returned to normal.

CASE 2

A 71 year old lady with disseminated sclerosis developed symptoms of lethargy, anorexia, and malaise two months after starting dantrolene (initially 25 mg/day increasing to 300 mg/day). The serum bilirubin remained within normal limits, but the AST rose to 137 IU/l and the AP to 320 IU/l. Treatment was immediately discontinued, the symptoms rapidly resolved, and the liver function tests were found to be entirely normal six weeks later.

CASE 3

An 80 year old lady with spasticity resulting from a hemiplegia had been taking dantrolene for three months (initially 25 mg/day increasing to 100 mg/

Table Relevant clinical data and results of liver function tests (maximal abnormalities recorded)

Case	Diagnosis	Age	Sex	Dantrolene		Bilirubin (μ mol/l)	AST (IU/l)	AP	Prothrombin time (s prolonged)
				Dose (mg/day)	Duration of therapy				
1	Familial tremor	64	M	100	4 w	320	550	171	9
2	Disseminated sclerosis	71	F	300	2 m	11	137	320	0
3	Hemiplegia	80	F	100	3 m	16	800	345	0
4	Disseminated sclerosis	45	F	150	3 m	10	245	50	0

day) when the routine screening revealed that the AST had risen to 145 IU/l with an alkaline phosphatase of 120 IU/l. Treatment was discontinued but the abnormalities progressed during the next six weeks with maximum changes of 800 IU/l for the AST and 345 IU/l for the AP. The serum bilirubin remained normal and two months later the AST and AP returned to normal. She never had any symptoms attributable to liver disease.

CASE 4

In a 45 year old lady with disseminated sclerosis, liver dysfunction was also detected on the routine screen three months after taking dantrolene (initially 25 mg/day increasing to 150 mg/day). The AST was found to be 245 IU/l with normal values for both the serum bilirubin and AP. She also had no symptoms. Dantrolene was discontinued and within four weeks the AST had fallen to 45 IU/l and to a normal value of 22 IU/l at five months.

ANALYSIS OF HISTOLOGICAL FINDINGS ON LIVER BIOPSY

A percutaneous needle biopsy (Trucut, Travenol) was performed at a time when the liver function tests were maximally abnormal in cases 1, 2, and 3 and in case 4 two weeks later when the AST had fallen from 245 to 125 IU/l.

The most striking changes were those of an acute hepatitis with spotty necrosis and/or areas of collapse of the reticulin, ballooning of liver cells, unusually marked pleomorphism of liver cell nuclei, and collections of pigment laden macrophages. The degree of necrosis was relatively mild in cases 1 and 2, while cases 3 and 4, despite the absence of any symptoms of liver disease or jaundice, had confluent centrilobular necrosis, and bridging necrosis was present in case 4 (Fig 1).

In addition, there were other features resembling those of an ascending cholangitis with a prominent inflammatory infiltrate, consisting mainly of poly-

Fig. 1 Liver biopsy in case 4 illustrating bridging necrosis between central area (C) and portal tract (P). Haematoxylin and eosin, $\times 80$.

morphs, within the portal areas and only minimal 'spillover' at the limiting plate. These changes were especially marked in cases 1 and 3 (Fig. 2). In case 1 there was also striking oedema of the portal areas

together with marked reduplication of bile ductules simulating extrahepatic biliary obstruction (Fig. 3). Eosinophils were identifiable within the portal tract infiltrate in all cases, but not to a marked degree.

Fig. 2 Case 3. Marked mixed cell infiltrate in the portal tract, with collections of polymorphs around bile ductules. Haematoxylin and eosin, $\times 250$.

Fig. 3 Case 1. Liver biopsy illustrating enlarged, oedematous portal area containing proliferated bile ductules together with a predominantly polymorph infiltrate. Haematoxylin and eosin, $\times 80$.

Discussion

The development of abnormal liver function tests in these four cases at one to three months after starting dantrolene, together with the resolution of the abnormalities after discontinuing therapy, point to the drug as the cause for these changes. Furthermore, in none of the cases could other causes be identified. Rechallenge with dantrolene, although not carried out in the present cases, has resulted in a recurrence of the liver damage in other reports (Ogburn *et al.*, 1976; Utili *et al.*, 1977).

The most striking of the histological changes—namely, the features of an acute hepatitis—have been observed by others (Ogburn *et al.*, 1976; Schneider and Mitchell, 1976; Utili *et al.*, 1977), but what was surprising was the marked dissociation between the severity of the histological changes and the clinical presentation. Cases 3 and 4, although asymptomatic, showed marked hepatic necrosis, whereas case 1 who had a severe clinical illness had only relatively minor hepatocellular changes. A dense portal tract infiltrate was also a feature in two other reports (Schneider and Mitchell, 1976; Utili *et al.*, 1977), but the predominance of polymorphs with a picture closely resembling ascending cholangitis has not been commented on. The associated 'hepatitis' and the lack of any clinical evidence or cause for an ascending cholangitis make coincidental biliary infection unlikely. Similar changes may rarely occur in acute viral hepatitis and have been referred to as 'cholangiolitic hepatitis' (Watson and Hoffbauer, 1946). In case 1 there were additional portal tract changes of marked oedema and bile duct reduplication, features typical of extrahepatic biliary obstruction. Cholangiography was not performed in the present case, but the disproportionately raised AST, together with the histological changes of a hepatitis in the liver parenchyma, are unlike those due to extrahepatic obstruction.

In five of nine cases reviewed by Utili *et al.* (1977) the histological changes were typical of chronic active hepatitis and three of these also had cirrhosis. In one of these the first liver biopsy was carried out five months after starting treatment and a further biopsy two years later showed progression to cirrhosis. The duration of treatment in the other cases was not stated. In cases 3 and 4 in the present study liver damage might not have been detected without routine liver function tests. It is conceivable that the lesion could have progressed insidiously to a chronic hepatitis and cirrhosis had the dantrolene not been discontinued.

Whether dantrolene sodium associated liver injury is a dose-related direct hepatotoxicity or idiosyn-

cratic is not clear. In the study of Utili *et al.* (1977) in which 1044 patients were monitored, there was no evidence for liver dysfunction when the daily dose was less than 200 mg, but three of the present cases were receiving only 150 mg or less. A recent survey of 671 patients receiving dantrolene failed to show any relationship between the occurrence of liver damage and dose (Hooper and Briscoe, in preparation). The presence of eosinophils within the portal tracts are often considered to indicate an allergic reaction but these were relatively few in number in our cases and they may also occur in acute viral hepatitis. The chemically related drug phenytoin has also been reported to cause a hepatitis, but, in contrast to dantrolene, this has usually been associated with other more generalised manifestations of an allergic reaction, such as rash, lymphadenopathy, and eosinophilia (Harinasuta and Zimmerman, 1968).

In the two large surveys referred to no relationship between the duration of treatment with dantrolene and the development of liver injury could be detected (Utili *et al.*, 1977; Hooper and Briscoe, in preparation). In view of the present finding that relatively marked histological evidence of acute liver injury may occur without associated symptoms, and that cirrhosis may develop insidiously (Utili *et al.*, 1977), monitoring of liver function tests at regular intervals (three monthly would be practical) would appear to be mandatory for all patients on long-term treatment.

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