Disulfiram-induced hepatitis—report of a case and review of the literature

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Summary
Disulfiram has been used as an adjunct to the treatment of chronic alcoholism since 1948. We report a young woman who developed clinical, biochemical and histopathological signs of a liver hypersensitivity reaction. A review of the literature is also presented.

KEY WORDS: disulfiram, hepatitis, hypersensitivity.

Introduction
Disulfiram, tetraethylthiuram disulphide was introduced in 1948 (Hald and Jacobsen, 1948) as an adjunct to the treatment of chronic alcoholism. The following year it was suggested that disulfiram might cause liver damage (Knutsen, 1949) and further evidence for its hepatotoxicity has since been published. Disulfiram has also been used as a chelating agent in the treatment of nickel dermatitis and in a few of these patients elevated serum transaminases have been recorded (Kristensen, 1981; Kristensen and Christensen, 1981).

The purpose of this article is to report the case of a young woman who developed hypersensitivity liver damage following oral disulfiram administration and review the published reports of disulfiram-induced liver disease.

Case report
The patient is a 32-year-old woman in whom retroperitoneal fibrosis was diagnosed in February 1978. It resolved completely on corticosteroid treatment. Due to an increasing alcohol consumption disulfiram treatment was started in August 1981. The dosage was 400 mg every 2nd day. Two months later she noticed small acneform eruptions on her legs, which later became generalized, and pruritus. One month later she developed chills and fever.

The patient was admitted in January 1982 and the disulfiram treatment was stopped. A generalized erythema with desquamated areas on the skin was seen. Laboratory analyses revealed an iron-deficient anaemia, elevated serum aspartate aminotransferase 5-0 μkat/litre* (normal <0-70), alanine aminotransferase 3-8 μkat/litre (normal <0-70) and alkaline phosphatase 24-85 μkat/litre (normal <5-0). Serum lactic dihydrogenase was elevated 10-8 μkat/litre (normal <7-5), but returned to normal level after 2–3 weeks. The serum bilirubin was normal and remained so. The erythrocyte sedimentation rate was normal throughout. Initially eosinophilia was present (12%) with a white cell count between 10-3 and 18×10⁹/litre. Serum amylose was normal. Increased IgA 4-1 g/litre (normal 1-2–3-5), IgG 14-5 g/litre (normal 7-0–14-0) and hypoalbuminaemia (30 g/litre) existed. Plasma haptoglobin was 3-0 g/litre (normal 0-45–2-7). Hepatitis B surface antigen, Wasserman reaction and Coombs’ test were negative. Antibodies against smooth muscle and mitochondrion type M₁ were positive at 1/25. Scintigraphy revealed no, hepatomegaly. The patient was transferred to the dermatology department, because of the severe dermatopathy, which persisted for about 6 months. A skin biopsy showed a non-specific dermatitis with infiltration of eosinophils.

A liver biopsy showed preserved lobular architecture (Fig. 1). The most distinctive alterations were found in the portal tracts, which were enlarged. There was mono and polymorphonuclear cell infiltration with eosinophils, slight proliferation of the bile ducts and increased fibrosis in some of the portal tracts. Connective tissue septa extended from the tracts but did not link with other septa.

Seven months later serum transaminases and alkaline phosphatase were normal. Antibodies against smooth muscle and mitochondrion were negative. The serum IgG and IgA levels were normal. The patient refused a further liver biopsy.

Discussion
A disulfiram hypersensitivity reaction was diagnosed in this patient on the basis of extrahepatic allergic manifestations namely rash, fever and eosinophilia. The liver biopsy showed inflammation of portal tracts with eosinophils, but absence of paren-
chymlal damage. No other drugs had been given. There was a possible predisposition to developing hypersensitivity reactions in that retroperitoneal fibrosis might be included in the group of hypersensitivity disorders and may cause sclerosing cholangitis (Bartholomew et al., 1963; Hellstrom and Perez-Stable, 1966). However, neither the liver biopsy nor the clinical course was compatible with this latter diagnosis. Five patients have been challenged with disulfiram and all developed sign of hepatic involve-
ment again (Kristensen, 1981; Keeffe and Smith, 1974; Eisen and Ginsberg, 1975; Ranek and Buch Andreasen, 1977; Morris et al., 1978). Challenge with the drug in our patient has not been performed because of the severe dermatopathy.

Since the first report of disulfiram-induced liver damage in 1949, a further 20 cases have been reported. Nine patients developed hepatic coma and died (Knutsen, 1949, Ranek and Buch Andreasen, 1977; Koborg and Søgaard, 1981). Extrahepatic manifestations seem to be scanty. Mitochondrial antibodies have not been recorded in any of these cases. The commonest clinical and laboratory data are summarized in Table 1.

Goyer and Mayor (1979) studied 50 men during hospitalization in an in-patient alcoholism rehabilitation unit. They failed to show a significant differences in liver laboratory parameters between disulfiram-treated subjects and controls.

From a histopathological viewpoint infiltration of

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**TABLE 1. Summary of clinical and laboratory data of disulfiram-induced liver damage reported in the literature.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration of treatment</th>
<th>Jaundice</th>
<th>Pruritus</th>
<th>Coma</th>
<th>Rash (1)</th>
<th>Fever (2)</th>
<th>Eosinophilia (3)</th>
<th>ASAT</th>
<th>ALAT</th>
<th>ALP</th>
<th>Bilirubin</th>
</tr>
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<tr>
<td>Knutson, 1949</td>
<td>4 weeks*</td>
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<tr>
<td>Keeffe &amp; Smith, 1974</td>
<td>10 days</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Eisen &amp; Ginsberg, 1975</td>
<td>4 weeks</td>
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<td>+</td>
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<tr>
<td>Ranek &amp; Buch Andreasen, 1977</td>
<td>2 weeks*</td>
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<tr>
<td>Ranek &amp; Buch Andreasen, 1977</td>
<td>6 months*</td>
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<tr>
<td>Ranek &amp; Buch Andreasen, 1977</td>
<td>4 weeks*</td>
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<tr>
<td>Ranek &amp; Buch Andreasen, 1977</td>
<td>8 weeks*</td>
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<tr>
<td>Ranek &amp; Buch Andreasen, 1977</td>
<td>3 weeks*</td>
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<td>+</td>
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<td>Ranek &amp; Buch Andreasen, 1977</td>
<td>12 weeks*</td>
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<tr>
<td>Morris et al., 1978</td>
<td>3 weeks</td>
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<tr>
<td>Vazquez &amp; Pardo, 1979</td>
<td>12 months</td>
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<td>Minden, 1979</td>
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<td>Kristensen, 1981</td>
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<td>Holm-Bentzen et al., 1981</td>
<td>12 weeks*</td>
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<td>Koborg &amp; Søgaard, 1981</td>
<td>6 weeks</td>
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<tr>
<td>Kristen &amp; Christensen, 1981</td>
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<td>Wise, 1981†</td>
<td>8 weeks</td>
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ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; ALP = alkaline phosphatase.

*The patient died.
†Further two patients were recorded, they developed coma and died.
‡Three patients reported to the author from the North Little Rock Veterans Administration Alcohol Treatment and Rehabilitation Unit.
infiltrates but otherwise normal liver structure, van Gieson (×50).

Inflammatory cells in the portal tracts have been found to be a common sign. In 3 cases focal necrosis ( Ranek and Buch Andreasen, 1977; Morris et al., 1978) were present and in one mild cytoplasmic degeneration ( Keeffe and Smith, 1974). In a Spanish report of 3 chronic alcoholic patients treated with disulfiram, hepatocytes were found to contain inclusions rich in filaments and scarce in glycogen granules. They were interpreted to be identical to Lafora's bodies (Vazquez and Pardo-Minan, 1979).

The diagnosis can be considered established if other hepatic diseases are excluded or readministration of disulfiram reproduces the symptoms. Patients with a known allergic history perhaps may be more prone to develop drug-induced liver hypersensitivity reaction. In such patients serum transaminases and alkaline phosphatases should be measured at short intervals. Disulfiram-induced hepatitis may be extremely rare or alternatively, disulfiram-related hepatic disease may have been overlooked because of the high prevalence of alcoholic liver disease in the population treated with disulfiram.

References


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