

BEST CLINICAL PRACTICE

Preventing disulfiram hepatitis in alcohol abusers: inappropriate guidelines and the significance of nickel allergy

COLIN BREWER¹ & FINN HARDT²

¹The Stapleford Centre London, UK & ²Department of Medical Gastroenterology, Copenhagen University Hospital, Hvidovre 2650, Copenhagen, Denmark

Abstract

Disulfiram hepatitis, although sometimes fatal, is a very rare complication of alcoholism treatment. A disproportionate number of cases are associated with disulfiram treatment for nickel allergy and unrecognized nickel sensitivity may partly explain the surprisingly high proportion of female victims – about 60%. US guidelines formulated in 1988 suggest that alcoholic patients should not be started on disulfiram unless liver toxicity tests have been done and, if elevated, returned to normal. This advice is unsound and contrasts with medical attitudes to the prevention of other rare side effects. It has led to significant delays in starting treatment which are probably much more hazardous than the very slight risks of hepatotoxicity. We recommend that the guidelines be modified in favour of an approach which emphasizes the education of patients and their carers and clinical rather than laboratory monitoring.

Introduction

Like many useful drugs, disulfiram is occasionally toxic to the liver. Its overall organ toxicity was rated as “intermediate” in a recent study using data from the Danish adverse drug reaction (ADR) index.¹ During 1968–91, there were 124 reports involving 154 ADRs to disulfiram. In about 40% of cases the liver was involved and, in about 15%, the skin. Fourteen deaths were due primarily to hepatotoxicity, corresponding to a rate of one death per 25 000 treatment years. Wright *et al.*² arrive at a similar figure, although Phillips³ believes that, in alcoholism treatment, “the true incidence is considerably lower”. In several cases, disulfiram was prescribed not to

deter alcohol use but as a chelating agent to treat nickel allergy.⁴

When disulfiram is prescribed in alcoholism, many patients will already have suffered some alcoholic liver damage and physicians are naturally concerned about the risk of adding one pharmacological hazard to another. Dupuy *et al.*⁵ do not regard abnormal liver toxicity tests (LTT) as a contraindication to disulfiram and emphasize the rarity of disulfiram toxicity but they advise that LTTs should be “monitored twice a month during the first two months”. However, unofficial US guidelines suggest that no patient should be started on disulfiram unless LTTs have been performed and, if elevated, have returned to

Correspondence to: Colin Brewer MB, MRCPsych, The Stapleford Centre, 25a Eccleston Street, London SW1W 9NP, UK. Tel: (44) 171 823 6840; Fax: (44) 171 730 3409; e-mail: cb@stap-cen.demon.co.uk

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normal. Subsequently, LTT monitoring should be frequent.²

This has led to an ironic development. There is unopposed evidence from several controlled trials – including one⁶ frequently singled out for its exemplary methodology⁷ – showing that disulfiram can be a highly effective intervention in alcohol abuse. However, it is underused for a variety of reasons.⁸ Initially, authorities on the alcoholism treatment effectiveness literature were reluctant to acknowledge its usefulness.⁹ This was due mainly to their failure to distinguish between trials in which the administration of disulfiram was supervised and those in which no third party was involved.

Having finally been persuaded,^{10–12} some of them now complain that even when dealing with patients whose lives are being seriously affected by alcohol abuse, they cannot get doctors to prescribe disulfiram without waiting for the results of LTTs.¹³ By the time these can be arranged, some patients have suffered further severe alcohol-related harm or have merely become drunk yet again and failed to keep their follow-up appointment, causing further delay. The guidelines must have made many doctors reluctant to prescribe disulfiram at all for the numerous alcoholic patients who have at least mildly abnormal LTTs, especially in the United States.¹⁴

Most studies show that when disulfiram is given to patients with abnormal liver function tests the abnormalities rapidly disappear. The occasional exceptions nearly always prove to be patients who are continuing to drink because they have stopped taking disulfiram or are taking an inadequate dose, or who have metabolic idiosyncrasies which make the reaction with alcohol insufficiently aversive. The only study to suggest otherwise¹⁵ found that in about 25% of patients treated with disulfiram, one of four liver enzymes, which initially were within normal limits, showed modest rises in patients who appeared not to be drinking. However, nothing in the study suggests that this finding indicated significant hepatotoxicity and other large studies have been much less alarmist.¹⁶ In some patients with severe alcoholic liver disease, disulfiram may have less effect because impaired liver function reduces the conversion of disulfiram into one of the many putative active metabolites.^{17–19} However, this lack of effect is not invariable and in Denmark, disulfiram is

regarded as potentially life-saving in cirrhotics who find it difficult to abstain.²⁰

Further evidence for the prevailing view that disulfiram toxicity is idiosyncratic rather than dose-related comes from a small group of 43 patients receiving supervised disulfiram in doses up to 1 g daily (average 363 mg) for an average of 7.6 months. In all patients who had abnormal LTTs at the start of treatment, LTTs improved while they were taking disulfiram. Among the nine patients taking 500 mg or more daily, in no case was there even a slight elevation of previously normal LTTs.²¹

The nickel factor

Nickel is extremely toxic. Disulfiram profoundly affects the retention and distribution of nickel,^{22,23} and has been used for many years as a chelating agent for nickel allergy or poisoning.²⁴ However, although it removes nickel by forming lipid-soluble complexes which are eventually excreted, there is initially an *increase* in tissue levels. Disulfiram may briefly reactivate dermatitis at sites of previous nickel contact but unlike a classic drug eruption, it disappears if disulfiram is continued.²⁵ Zala *et al.*²⁶ suggest that disulfiram's ability to mobilize and chelate lead, which then crosses the blood–brain barrier, may explain some organic psychosyndromes associated with disulfiram, rare though these are. In mice given disulfiram and nickel, nickel levels in brain are as much as 700 times higher than in controls but concentrations in liver are also quite high.²³

Kaaber *et al.*⁴ report a series of 58 women and three men with nickel allergy and hand eczema treated with disulfiram. They carried out their study because they “felt there was a surprising rate of hepatotoxicity” and it was indeed “the most significant side effect. Five patients had evidence of hepatitis; for four of these, the symptoms were so severe that the patients had to be hospitalised.” Liver biopsy in four cases showed acute hepatitis. Six other patients developed raised serum aminotransferase activities. They conclude that “hepatotoxicity is a frequent side effect of disulfiram treatment [for] nickel allergy”, and that disulfiram should be reserved for severe, treatment-refractory cases. However, “none of the patients had sequelae to the liver damage” and the risk was not dose-related.

This 8% incidence of hepatitis in nickel allergy misleadingly inflates the ADR figures. Kaaber *et*

*al.*⁴ note the "sharp contrast to the few reported side effects when alcoholic patients are treated with disulfiram" but point out that in many countries, "10% of the adult female population is sensitised to nickel" [our italics], presumably from wearing costume jewellery. This raises the interesting and clinically important possibility that some cases of disulfiram hepatitis in alcoholism treatment are due to unrecognized nickel sensitivity. Since men considerably outnumber women in most alcoholism clinics, nickel sensitivity may also explain the disproportionate number of female cases in literature surveys by Wright *et al.*² – nine of 17 – and by Zala *et al.*²⁶ – 13 of 24. Although Dupuy *et al.*⁵ note that 60% of reported cases involved women, this important epidemiological feature is generally ignored. The possible role of nickel sensitivity in alcoholic patients receiving disulfiram does not seem to have been mentioned previously.

Comparative hepatotoxicity of disulfiram and other drugs

Many drugs cause hepatotoxicity which is sometimes lethal. Chlorpromazine (CPZ) is a relevant example. It is still sometimes used in non-delirious alcohol withdrawal because it is perceived as less potentially addictive or abuseable than sedatives such as benzodiazepines or chlormethiazole, even though it increases the risk of withdrawal seizures.²⁷ Few clinicians would assert that it should not be administered until liver toxicity tests have been performed, even though cholestatic jaundice occurs in 1% of CPZ-treated patients.²⁸ Indeed, Kaplowitz *et al.*²⁹ conclude that CPZ " . . . is intrinsically toxic with sub-clinical cholestasis occurring in most patients".

Paracetamol is often preferred to aspirin as a simple analgesic for alcoholic patients because it causes less gastric irritation. However, even in normal therapeutic doses ($\leq 4\text{g/day}$) it can cause acute liver failure in alcohol abusers. Zimmerman & Maddrey³⁰ reported 67 cases and reviewed another 94 reported previously. Mortality was nearly 20%. They note that many physicians and alcoholic patients seem unaware of the risk.

If physicians took the view that no alcoholic patient with even mildly abnormal liver function tests should be prescribed drugs which have a

hepatotoxic potential similar to or greater than that of disulfiram, then the medical treatment of many of the conditions from which alcoholics suffer (whether as a consequence of alcohol abuse or simply as concomitant illnesses) would become very difficult. Other drugs they would have to avoid include isoniazid, erythromycin, valproic acid, intravenous tetracycline, nitrofurantoin and methotrexate.

Protection against alcoholic liver damage by disulfiram treatment

In most alcoholic patients with disorders of liver function, the disorders are due directly and exclusively to their excessive alcohol intake. In so far as the prescribing of disulfiram prevents or reduces this excess, it will allow the liver to recover from alcoholic poisoning. In a proportion of cases, this protection from alcoholic hepatotoxicity will save the patient from serious hepatic insufficiency or death. These benefits need to be balanced against the very small risk of disulfiram hepatotoxicity. Many patients stop drinking or reduce their alcohol consumption to much less harmful levels without the need for disulfiram, but if they continue to drink excessively despite compliance with standard non-pharmacological treatment programmes, then disulfiram should at least be offered to them.³¹ Some clinicians go further and decline to continue providing psychosocial interventions for patients who continue to drink unless they accept supervised disulfiram.³²

In general, therefore, disulfiram is given to patients who fear, or have already demonstrated, that they cannot abstain for long (or at all) without it. To deny such patients the benefits of disulfiram on the grounds of an extremely low risk of hepatotoxicity is rather like declining to operate on a medication-resistant gastric ulcer or lumbar disc lesion because the occasional patient will die from unexpected complications of surgery or anaesthesia. Black & Richardson³³ describe a well-investigated case of disulfiram hepatitis in a patient who recovered but resumed drinking when disulfiram was discontinued. They conclude: "The apparent incidence of . . . hepatotoxicity is very low and should not deter the clinician from using this drug . . . in alcoholic patients in whom the risk of continued drinking is high."

Reversibility of disulfiram hepatitis

In all reported cases, including fatal ones, so-called "fulminating" disulfiram hepatitis (from the Latin *fulmen* = lightning) had a relatively gradual onset over at least a few days. In most cases patients recovered, as they did in eight reported cases where the diagnosis was confirmed by a further challenge with disulfiram. In all reports, it was obvious on *clinical* grounds (even if sometimes with the benefits of hindsight) that the patient was becoming unwell and most of the typical signs of hepatitis were present. No patient appears to have died if disulfiram was discontinued as soon as the first signs of jaundice became apparent.³⁴

Most alcohol-related cases seem to have occurred in patients who did not have much medical supervision during the first few weeks of treatment when the onset is most likely. Consequently, the complications began and progressed unnoticed until they became severe. In contrast, the dermatological cases appear to have had weekly follow-up at the start of treatment. In none of the reports is there any indication that patients were given routine information about possible side effects to encourage recognition at an early stage.

Only one reported case of clinically obvious disulfiram hepatitis has ever developed after only a few days treatment. Although disulfiram hepatotoxicity is not generally thought to be dose-related, it may be relevant that the disulfiram dose – 1.5–2 g daily – was the highest of any reported case.³⁴ The average latency, according to a recent review, is 41 days.²⁶ In one of the most rapidly developing reported cases, jaundice was noticed after 13 days of disulfiram treatment at 250 mg daily, but disulfiram was continued for a further 5 days and although baseline liver toxicity tests had been performed, no further tests were performed until the 18th day.²⁶

Obtaining blood for baseline liver toxicity tests (and other markers of alcohol abuse, such as mean corpuscular volume and carbohydrate-deficient transferrin) is sound practice when starting treatment with disulfiram. It is also sound practice before starting any other sort of treatment in alcohol abuse, given the poor reliability of self-reports as a measure of progress. A sample should be obtained ideally before the first dose of disulfiram but it seems unlikely to matter if the sample is not obtained until 2 or 3 days after the first dose.

False alarms

Salvato & Mason³⁵ report a case of seemingly iatrogenic hepatotoxicity during nalmefene treatment for alcoholism which was probably due to eating chilli. Despite a seven-fold increase in alanine amino transferase nalmefene treatment was continued, since the patient was not unwell, and the LTT abnormalities disappeared after 4 weeks. They note that a hazard of frequent LTT monitoring is that "such a broad net is cast that 'normal' fluctuations in LTTs are captured in the data collection process and incorrectly attributed to the medication . . . Such an incorrect attribution could easily be made by a narrowly focused investigator or clinician, resulting in possible termination of [an effective] drug". They urge clinicians to avoid such "reflexive" responses to abnormal LTTs.

A better approach

It is instructive to compare and contrast the disulfiram guidelines with physicians' attitudes to rare haematological side effects. A recent review argues that "for drugs with a known but rare association with agranulocytosis (e.g. cephalosporins, NSAIDs) the rarity and unpredictability of the reaction makes regular, routine monitoring not worthwhile" and notes that as many as one in 1300 patients treated with CPZ develop agranulocytosis.³⁶ Occasional cases of aplastic anaemia – which is quite often fatal – occur as an uncommon idiosyncratic reaction to many commonly prescribed psychotropics, not to mention the special case of clozapine, which is much more myelotoxic. Balon & Berchou³⁷ state that

" . . . routine blood tests have not proven very useful in the prediction or early detection of these serious adverse effects . . . The most important precaution remains the physician's awareness of the possibility of such side effects and thorough evaluation of any abnormality during treatment . . . In addition to clinical monitoring, *advising patients about the possibility of haematologic side effects and instruction to contact their physician should any of these symptoms occur* may be helpful in avoiding a fatal outcome" [our italics].

We submit that this approach, supported by Phillips³ and mentioned briefly by Wright *et al.*,² which emphasizes information-giving and the clinical monitoring of the whole patient, is a more

Table 1. Revised guidelines for preventing disulfiram hepatitis in alcohol abusers

1. Ask patients about possible nickel sensitivity before starting treatment with disulfiram
2. It is often important to start disulfiram treatment promptly in a patient who has just managed, with difficulty, to get alcohol-free. Treatment can be started without waiting for the results of liver-toxicity tests (LTTs)
3. Assuming prompt reporting by the laboratory, it does not matter much whether a blood sample is drawn just before, or a day or two after, starting disulfiram
4. Warn patients that disulfiram, like most useful drugs, can occasionally cause serious side-effects. They can be given simple information about early symptoms of neuropathy and liver disease, especially the importance of dark urine
5. Patients starting disulfiram treatment for the first time should be reviewed at appropriate intervals by a doctor, or by suitably trained nurses or counsellors. They should be encouraged to report in person or by telephone if they think they may be experiencing side effects
6. A further sample for alcohol abuse markers, including LTTs, should be taken at about 4 weeks, or at any time if there are clinical grounds for suspecting hepato-toxicity
7. Patients who have tolerated previous disulfiram courses without side effects should receive the same warnings but may need less monitoring of LTTs

appropriate response to rare and unpredictable drug reactions. Dark urine is *always* one of the early signs of acute liver failure and precedes obvious jaundice. In addition, patients should perhaps be asked about nickel sensitivity when disulfiram is prescribed, especially if female. There is no evidence that the guidelines suggested by Wright *et al.*² have saved a single patient from death or serious illness and if Balon & Berchou³⁷ are right, they are not likely to do so. However, if Meyers¹³ is right, the guidelines are already causing avoidable harm and are likely to cause the occasional death. "First do no harm" is an admirable maxim, but harm can be done by doing nothing as well as by doing the wrong thing. The 10-year mortality rate in alcoholism is often 10–20% in follow-up studies (Table 1).

Phillips³ notes that Wright *et al.*² "have not evaluated their proposed new guidelines in a prospective clinical trial" and that "guidelines with no proven clinical value may establish a meaningless 'standard of care' which, in the long

run, could be of less value than no guidelines at all". Wright *et al.* concede that there is absolutely no evidence that patients with even markedly abnormal liver functions are more at risk of experiencing disulfiram hepatotoxicity than those with no or slight abnormalities. McCormick³⁸ observes that:

"Guidelines derive from population studies and are not always applicable to the unique person who decides to consult. All might be well if guidelines were securely based and if they were perceived as giving advice rather than mandatory instruction. Unfortunately, many guidelines are insecurely based, and doctors, sometimes fearing medico-legal consequences, are motivated towards slavish adherence to them".

The guidelines for disulfiram should be changed.

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