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Safety Issues Concerning the Use of Disulfiram in Treating Alcohol Dependence

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Contents

Abstract

Disulfiram is known to cause hepatitis, which is sometimes fatal. The best estimate of the frequency of disulfiram-induced fatal hepatitis is 1 case in 30 000 patients treated/year. Its appears to be more common in patients given disulfiram for the treatment of nickel sensitivity. Frequent blood testing for liver function is probably not necessary, but patients taking disulfiram should be in regular contact with a physician.

There are rare reports of psychosis and confusional states in conjunction with disulfiram treatment and peripheral neuropathy and optic neuritis have been reported; these effects are dose-related. Psychiatric complications appear to be more common with the use of disulfiram in India than in Western countries. Of the less serious adverse effects, tiredness, headache and sleepiness are the most common.

Deaths from the disulfiram-alcohol (ethanol) interaction have not been reported in recent years, possibly because the dosages used are lower than those used 40 years ago, and patients with cardiac disease are now excluded from

treatment. There is no evidence to suggest that disulfiram causes cancer. Of note, there are drug interactions with compounds that utilise the cytochrome P450 enzyme system.

Disulfiram can be viewed as a drug with a moderate record of adverse effects. Alcohol dependence, for which it can be a helpful treatment, is associated with a high morbidity and mortality.

Alcohol (ethanol) dependence is a potentially fatal disorder, which often does not respond to medical or psychiatric intervention. Randomised controlled trials of disulfiram have shown that, when patients agree to involve a third party to assist their compliance, this deterrent approach can improve the outcome of treatment.[1] Since disulfiram was first prescribed for alcohol dependence in 1947, there have been concerns about its safety, namely the risks of the disulfiram-alcohol reaction and the risk of toxic effects of the compound on the nervous system and on the liver.

1. Search Procedure

The sources used in the following review were literature searches on Medline (publications from 1966; date of search, early 1998) and the Adis International comprehensive inhouse database; certain specific enquiries to the manufacturer; correspondence with the author of 1 paper; and manual searches from 1966 back to 1950 of Quarterly Journal of Studies on Alcohol, British Medical Journal, and the Journal of the American Medical Association. No exclusion criterion based on study methodology was applied: many papers were individual case reports, although weight was given to reports where re-exposure to disulfiram had replicated the adverse effect. Where a finding has been replicated in successive publications only the study or studies where the finding was most robust have been cited, or a relevant review paper.

2. Hepatotoxicity

The world literature of the last 40 years contains 30 reports of patients with hepatitis related to disulfiram. National Drug Adverse event registers would suggest there are also cases not written up and published. At the recommended dosage level, hepatotoxicity has been noted to occur as rapidly as 13 days after commencing the drug, and after a total dose of as low as 4.5g prescribed at 250 mg/day.[2] Sometimes the hepatitis has resolved on stopping the drug, but at other times a fulminant course has ensued. In some reversible cases, the causal relationship has been demonstrated by a challenge e.g. Morris et al.[3], Bartle et al.[4] Although people with alcoholism clearly have a high prevalence of liver disorders related to other causes, many of the cases of disulfiram-related hepatitis have occurred in patients who had normal liver function tests on commencing the medication. Hepatotoxicity has also been described in patients without alcoholism (disulfiram is sometimes prescribed for nickel sensitivity).[5]

2.1 Frequency

Denmark is probably the country in the world where, per capita, the most disulfiram is prescribed.[6] Reports to the Danish Committee on Adverse Drug Reactions from 1978 to 1987 of all drug-induced hepatic injury revealed that 35 (2.9%) of the 1188 reports were linked to disulfiram, as were 5 (10%) of 52 drug-induced hepatitis fatalities.[7]

However, the most important frequency estimate is of the risk per prescription of disulfiram. There is only 1 such published estimate, also from Denmark. Spontaneous reports of adverse drug reactions to disulfiram treatment were examined for the period 1968 to 1991.[8] There were 11 fatal liver reactions reported in 22 years. Using drug sales figures to estimate the number of patients taking disulfiram to be 15 000 per year, the reported risk of dying of hepatotoxicity caused by disulfiram can

be calculated to be 1 : 30 000 patients per year. Some of these were patients receiving disulfiram as treatment for nickel sensitivity, and it appears from 1 uncontrolled study[9] that the risk of liver disorders linked to disulfiram is vastly greater in these patients than in people with alcoholism, hepatitis occurring in 8% of such patients (nickel in the body is mobilised by disulfiram and can be deposited in the liver).

2.2 Timing

In the Danish data,[8] disulfiram-related hepatitis had commenced between 16 and 120 days after starting treatment, with a peak frequency at 60 days. However, in 1 case, a woman who had commenced taking disulfiram in excess of the prescribed dosage (she took 1.5 to 2 g/day) developed jaundice within 5 days.[10]

2.3 Mechanism

When liver function is monitored during disulfiram treatment, abnormalities in liver enzyme levels may occur but can often be attributed to resumption of drinking. There is 1 report which has shown more liver enzyme level elevations in patients taking disulfiram than in patients in the same programme who did not receive the drug (the Tri-Services Alcoholism Recovery Project study).[11] Allocation to disulfiram or no disulfiram was not random in the study. The clinic offered disulfiram 250 mg/day to all patients, but some were excluded for various reasons including any abnormal liver function test. Compliance was monitored. Patients were inpatients throughout the study period and were screened for use of alcohol at random by breath and urine alcohol tests. At 4 weeks into the study, the level of 1 or more transaminase had become elevated in 30% of patients taking disulfiram and in 11% of control patients. The levels of 2 or more transaminases were elevated in 9% of patients taking disulfiram. Two patients taking disulfiram, compared with none of the control individuals, had an elevation of ALT levels greater than 3 times the upper limit of normal, which is the level at which in other drug hypersensitivities the risk of hepatitis is significant.

Two studies where there was random allocation to disulfiram or a placebo have been published that give follow-up liver function test data. Iber et al.[12] followed 453 male patients for 1 year. In both studies abnormalities in liver function tests did not occur more frequently in the disulfiram patients than in control participants.[12,13] In only 1 of these 2 studies[13] was compliance with medication over 6 months ensured by supervision. In that study, liver enzymes levels showed an on average improvement in the disulfiram group but a deterioration (associated with more frequent alcoholic relapse) in the control participants.

Two reports provide long term data on hepatotoxicity from studies that did not include a control group. Borup et al.[14] reported data from 93 patients who had taken disulfiram for 1 year supervised by the clinic at a dosage of 600 to 800mg twice weekly. No patient developed liver function abnormalities. In a series of 43 patients receiving supervised disulfiram treatment in dosages up to 1 g/day (mean 363 mg/day) for a mean of 7.6 months, Brewer[15] reported that all patients who had abnormal liver function tests at the start of treatment showed improvement. Nine patients were taking 500 mg/day or more and in none of these patients was there even a slight elevation of previously normal liver function tests. In a study of 50 male inpatients randomised to receive either placebo, disulfiram 250 mg/day or disulfiram 500 mg/day no differences in liver function tests emerged.[16]

In a 12-week follow-up study of 57 men with alcoholism, some of whom had elevated transaminase levels and serological evidence of hepatitis C virus infection at commencement of disulfiram therapy, 1 patient showed an elevation of transaminase levels attributable to disulfiram, without clinical complications.[17]

It seems from the Tri-Services Project[11] that under some circumstances disulfiram is associated with an increase in liver transaminase levels, but the weight of evidence is that clinical hepatitis is

rare. There is no evidence that a pre-existing liver disorder increases the risk of disulfiram hepatotoxicity.[18] In most of the reported cases of patients with hepatitis the patients had normal liver function tests at the start of treatment. A fatal outcome was more likely when the drug was continued for some days after jaundice had been noticed.[10] Hepatitis may be due to accumulation of toxic metabolites[10] or in some cases due to the expression of autoantibodies directed against specific cytochrome P450 enzymes.[19]

2.4 Monitoring

There have been several attempts in the literature to specify when liver function in blood tests should be checked. In some treatment centres it became routine practice to assess liver function before and at frequent intervals during treatment with disulfiram (e.g. Wright et al.[11]). A recent single case report, where liver function testing at day 16 produced normal results, but jaundice had developed by day 42, led to another call for 2-weekly testing of all patients receiving disulfiram.[20] However, the onset of the hepatitis is usually very rapid, and so even frequent testing may not detect it. In addition, abnormal enzymes levels are commonly caused by a resumption of alcohol ingestion which might lead to unnecessary withdrawal of the drug. Thus, it can be argued that frequent blood test monitoring is unlikely to be productive, especially given the rarity of severe hepatotoxicity.[21]

In my view, informing the patient, the patient's relatives and the family practitioner, of the 1 in 30 000 risk of fatal hepatotoxicity, emphasising detection of jaundice usually preceded by fever, so that the drug is stopped when adverse effects are noticed, is probably an equally efficient way to prevent fatal hepatitis and still allow many patients to benefit from disulfiram treatment.

Brewer and Hardt[22] recommend that patients should be asked about nickel sensitivity before starting treatment with disulfiram and that liver function tests should be measured near the time of starting therapy (not necessarily in advance) and again after about 1 month.

In summary, hepatitis is very rarely a consequence of disulfiram use. Abnormal liver enzymes levels caused by alcohol use need not be a contraindication to the use of disulfiram. Indeed, when the patient is helped to achieve abstinence by taking disulfiram such abnormalities will probably resolve. However, patients should be informed about even very rare risks associated with drug therapy. Medical supervision of patients taking disulfiram should continue for as long as the patient uses it and should be at least monthly for the first 6 months. There is no compelling evidence to support repeated liver function testing as a way of preventing serious hepatotoxicity.

3. CNS Adverse Effects

3.1 Confusional States/Psychosis

There are occasional reports from Europe and North America of disulfiram-linked psychosis or a confusional state (beginning with fatigue and forgetfulness, rarely proceeding to ataxia or stupor). These reports were commoner in the early days of disulfiram therapy when higher dosages than are commonly used today (500 mg/day or more) were routinely prescribed. This potentially serious adverse effect may be more frequent in some countries than others. While only 4% of adverse drug reactions reported for disulfiram in a Danish database were psychiatric,[8] the WHO database when examined by Enghusen Poulsen et al.[8] showed that 13% of disulfiram adverse effects were psychiatric.

Two papers from India, Krishna Murthy and Praveenlal[23] and Krishna Murthy,[24] have described higher rates of disulfiram-induced psychosis arising *de novo* than other papers, with the effect starting 2 to 3 weeks after commencing treatment with disulfiram. Symptoms included overactivity, overtalkativeness, paranoid delusions, insomnia and auditory hallucinations. Symptoms usually completely resolved after withdrawal of disulfiram and sometimes after a short course of treatment with an antipsychotic drug. In 1 series, 6 cases of disulfiram-induced psychosis occurred in 52 pa-

tients,[23] and in the second series there were 5 cases of disulfiram-induced psychosis among 53 patients.[24] In all patients the dosage of disulfiram was 250mg twice daily. Another paper from India[25] described a series of 38 patients of whom 1 developed a confusional state while receiving disulfiram at a dosage of 250 mg/day. The adverse effect resolved and then recurred on each of 2 re-exposures.

The reason for the apparently high rates in India is unknown. One possibility is that the bioavailability of disulfiram manufactured locally may be different from the compound available in Europe and North America. Two cases of psychosis associated with disulfiram have been reported in Caucasian patients; however, the psychosis seemed to result from an interaction between cannabis and disulfiram.[26,27] The Indian papers do not mention concomitant cannabis, which is widely available in that country; however, Krishna Murthy (personal communication) states that cannabis use was not suspected in the patients in his reports.

In a North American series of 243 patients treated with disulfiram 250 mg/day, 5 patients had 'an organic brain syndrome' (which was not well defined in the paper).[28] In patients with alcoholism, psychiatric disturbances can be caused by drinking alcohol and can occur because of co-existing psychiatric disorders. Therefore, only a controlled study can provide a realistic estimate of the prevalence of unwanted psychiatric effects with disulfiram. In a follow-up study of 612 male North American patients randomised for 1 year to either disulfiram 250 mg/day, disulfiram 1 mg/day or placebo, the incidence of psychiatric complications was 2.4% in the disulfiram-treated groups, and the incidence was not significantly different between the groups.[29] No psychotic illness was diagnosed. This was a treatment outcome study, and previous psychotic illness had been an exclusion criterion. Thus, if disulfiram causes psychosis by precipitating a pre-existing illness, this would explain the absence of any psychotic adverse effects in this and in other placebo-controlled studies (e.g. Chick et al.[13]) where no psychiatric complications have been noted.

There has been 1 report of catatonia attributed to disulfiram therapy and this adverse effect is therefore presumably very rare.[30]

In the data sheet for disulfiram, previous psychosis is an exclusion for the use of this agent. However, alcohol misuse in schizophrenia can be very harmful to the patient and, lacking another effective treatment, clinicians weighing up the risks and benefits of treatment have sometimes recommended disulfiram in this context.[31] A wide-reaching review of all aspects of disulfiram use in patients with alcohol dependence and other psychiatric disorders that also looked at potential drug interactions, concluded that the rate of serious unwanted psychiatric effects was extremely low at recommended disulfiram dosages of 200 to 250 mg/day.[32]

The reason for a possibly higher rate of psychosis in India needs further examination.

3.2 Other Serious CNS Syndromes

A case report was published about a man who took disulfiram 250 mg/day for 30 years, and experienced a gradual decline thereafter in memory and performance IQ tests; this decline partially recovered on stopping the drug.[33] Peripheral neuropathy was also noted to have occurred. A positron emission tomography study,[34] which showed reduced cerebral metabolic rate for glucose in patients with alcoholism taking disulfiram compared with those not taking disulfiram, found no differences between the groups with respect to neuropsychological performance. No adjustments were made for differences in severity or duration of patients' heavy drinking in this study.[34] There are no published randomised controlled studies which have compared cognitive performance changes over the course of disulfiram use.

That very large doses of disulfiram might damage the basal ganglia is illustrated in 3 case reports by Laplane et al.[35] In 1 case report, a patient who took an overdose of 75 disulfiram 500mg tablets, developed parkinsonian symptoms and low den-

sity lesions of the basal ganglia, but made a full recovery. The second case was a young man who took disulfiram 1 g/day for 8 weeks, and his parkinsonian symptoms had not completely resolved at 19 months. The third case was a male patient who had taken disulfiram 500 mg/day for 'several months' and poor cognitive performance and apathy were attributed 12 years later by his family to the period of treatment with the drug. It must be emphasised that such reports are very rare.

4. Neuropathy

The earliest onset of neuropathy in a patient taking disulfiram was 10 days.[36] Most reports place the onset of symptoms as several months after commencing treatment and the peak time in the Danish data[8] was 1 year. The rate of disulfiram-induced neuropathy in that study can be estimated from the sales figures quoted for the reporting period of 22 years as about 1 in 15 000 patient years. Except in 1 patient, who was taking disulfiram 250 mg/day for 30 years,[24] the dosage in patients developing peripheral neuropathy has been 500 mg/day or more. Sometimes patients developing neuropathy have been taking other medications. For example, in 1 report the patient took the sedatives ethchlorvynol and triclofos (trichloroethyl phosphate), which are substituted alcohols.[37] Only 2 patients have developed neuropathy at our Edinburgh clinic after 18 years of treating several hundred patients. These 2 patients were also taking amitryptiline and both patients had on their own initiative been taking disulfiram 500 mg/day or more because at a dosage of 200 mg/day the alcohol-disulfiram reaction was insufficient to be a deterrent.

Systematic investigations of nerve function have found delayed nerve conduction without clinical signs of symptoms in patients taking disulfiram 250 mg/day but not at a dosage of 125 mg/day. Abnormalities develop during the first 3 to 6 months and seem not to have onset thereafter (reviewed by Enghusen Poulsen[8] and Dupuy et al.[38]).

The clinical presentation of disulfiram-induced neuropathy is usually a slow onset; however, acute onset over 24 hours has been described.[39] Recovery may be complete or partial, with residual symptoms such as foot drop or paraesthesia.

4.1 Pathology

Carbon disulphide is a metabolite of disulfiram and industrial exposure to this agent has caused neuropathy with axonal degeneration.[37] The pathology, as well as the clinical presentation of disulfiram-induced neuropathy, also resembles that seen in alcohol-induced neuropathy.

Since 1953, some 11 cases of optic neuropathy, apparently always reversible, have been described.[38]

In summary, 50 years of disulfiram use has established that neuropathy is a risk when higher dosages of disulfiram are administered, but this adverse effect is rare and reversible if detected early. Alerting the patient, even to rare risks, is advisable, and medical monitoring of patients is required.

5. Less Serious Adverse Effects

In controlled studies, the adverse effects which occur more frequently in disulfiram recipients than in control patients are tiredness, headache and sleepiness. Some patients' spouses report an unpleasant odour on the patient's breath. This is sometimes described as a garlic smell. However, in my experience usually the spouses state that they prefer to have a partner who is abstinent and has garlic-smelling breath than one who is drinking and has stale alcohol on the breath.

Skin complaints with disulfiram are rare. However, rashes, pruritus and exfoliative dermatitis have all been described in association with disulfiram. Although these skin complaints have been described as occurring after 1 year of treatment they tend to occur in the first 2 weeks of treatment. Early rashes sometimes clear without the need for treatment or discontinuation of disulfiram; displacement of nickel could perhaps explain the occurrence of skin complaints in some cases (discussed by Enghusen Poulsen et al.[8]).

6. The Disulfiram-Alcohol Interaction

Many patients taking disulfiram 200 to 250 mg/day risk experiencing the disulfiram-alcohol interaction by deliberately ingesting some alcohol. The severity of the reaction at these dosages varies from a slight flush to a distressing state of nausea, headache, dizziness and tightness in the chest. Very rarely, when larger amounts of disulfiram have been taken, the reaction has been fatal. These fatal cases, which only appear in the literature in the first 10 years following disulfiram's introduction, were examined in detail at the time. The patient described in the report by Becker and Sugarman[40] had been given 5g of disulfiram over 4 days and was then given 1oz of whisky (i.e. about 15g of alcohol). He experienced a hypotensive collapse, followed by 4 hours' recovery with some treatment. The patient then died suddenly of acute right heart failure. His coronary arteries showed some atherosclerosis but he had had a prior normal electrocardiogram (ECG) and exercise test. One of the cases investigated by Jacobsen[41] died some hours after the reaction had apparently been at its worst. In the days when patients were given a 'test' reaction, ECG studies showed that most patients developed some ECG changes during the reaction, usually prolongation of the QT interval. Hypotension is clearly a dangerous aspect of the disulfiram-alcohol reaction. However, hypertension has been described in a patient who also developed bronchospasm (he took 300ml of 4.1% lager after 6 days treatment with disulfiram 200 mg/day).[42]

The hypotension associated with the disulfiram-alcohol reaction is greater in older patients,[43] perhaps because the elderly have less cardiovascular tolerance to the toxic reaction. The hypotensive reaction is related to the level of acetaldehyde found in the blood during the reaction. It might be supposed that when liver function is poor, less acetaldehyde might be produced and therefore the disulfiram-alcohol reaction might be less in patients with liver disease. However, in a detailed study in 13 patients, variations in liver function did not help to explain the marked variations found in the severity of the disulfiram-alcohol reaction.[43]

There have been no reports of death due to the disulfiram-alcohol interaction in recent years.[44] This may be due to less reporting, but is perhaps more likely to be due to more cautious dosage and patient selection than in the early years of use.

Because of the potentially fatal outcome of a disulfiram-alcohol reaction in a patient with heart disease or a patient taking hypotensive medication, disulfiram should normally not be offered to such patients. This restriction would apply absolutely in a patient with heart disease who was still in the chaotic stage of alcohol dependence where there is mood disturbance and a risk that the patient might consume alcohol while taking disulfiram.

7. Intentional Overdosage

Patients with alcoholism are at high risk of drug overdose. Disulfiram overdose with or without the ingestion of alcohol has occurred on numerous occasions. Serious results seem to be very rare. A case of acute fulminant polyneuropathy following simultaneous ingestion of alcohol and a high dose of disulfiram has been described in by Rothrock et al.[45] and a case of basal ganglia damage has already been mentioned in section 3.2.[35]

Disulfiram should not be given to a suicidal patient. Despite this caveat, there are patients with alcoholism who take medication overdoses when they are intoxicated and in practice the use of disulfiram can significantly help patients not to drink and thereby reduces or stops this behaviour which is costly to the patient and to health service resources.

8. Drug Interactions

Drugs utilising the cytochrome P450 enzyme system in their oxidative breakdown will show augmented plasma concentrations and longer elimination half-lives if the patient is taking disulfiram. This has been demonstrated for amitryptiline, imipramine, warfarin and phenytoin and will apply to other agents such as, for example, benzodiazepines such as chlordiazepoxide and diazepam, though not lorazepam and oxazepam.[46] A case of delirium with concomitant administration

of phenytoin and disulfiram has been described.[47] An interaction with omeprazole has been reported that resulted in confusion with catatonia, and this was effect was reproduced at a second supervised re-exposure to the two drugs.[48]

Regarding a possible interaction with paracetamol (acetaminophen), a review of 2 studies in rats and 1 in humans suggest that there is no hazardous reaction.[8] Paracetamol overdose is especially poisonous in overdose in patients with alcoholism and theoretically disulfiram might reduce its toxic effect on the liver.

9. Cancer

A long-term, Swedish follow-up study found that 14 out of 24 individuals who had died of neoplasm (mainly lung) had received disulfiram treatment, while among the other 142 deaths only 47 had received disulfiram.[49] This association with lung cancer was almost certainly spurious: the patients with more severe alcoholism in that sample had received disulfiram, and I believe would also have been the heavier smokers. An earlier Canadian mortality study found lung cancer deaths to be lower in those treated with disulfiram.[50] There is therefore no evidence that disulfiram causes cancer.

10. Overall Conclusions

Alcohol dependence is associated with high rates of minor symptoms, numerous serious pathologies and an age-related mortality risk 3 times that of the general population. It is to be expected that a drug used in the treatment of alcoholism might become a suspect cause of some of the adverse consequences of alcoholism, and careful disentangling of causal and noncausal association is needed, as for example in the case of cancer and disulfiram. However, disulfiram can cause fatal hepatitis, albeit very rarely, and can cause neuropsychiatric and skin complications. Taken together, these amount to a frequency of 1 case per 200 to 2000 patients per year.[8] Serious hepatotoxicity and neuropathy probably occur at less than 1 case per 10 000 patients per year. This does not place disulfiram among the high risk category for adverse drug reactions.

There is no unanimity among authors or manufacturers on what monitoring should be in place for early detection of the adverse effects of disulfiram. It has been recommended that greater vigilance is needed in female than male patients[38] and the probable dose relationship for neurological adverse drug reactions should dictate greater vigilance whenever the dosage exceeds 250 mg/day. Clearly, all patients taking disulfiram should seen regularly by a physician at a minimum time interval of every 2 weeks for the first 2 months and monthly thereafter. Patients should be advised that there are some serious rare adverse effects associated with disulfiram treatment and to report any unexplained symptoms immediately. They can also be told that disulfiram can be a very helpful aid in recovery from alcoholism.

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