Precautions

Disulfiram is contra-indicated in the presence of cardiovascular disease or psychosis or severe personality disorders, and should not be given to patients known to be hypersensitive to it or to other thiuram compounds, such as those used in rubber vulcanisation or pesticides. It should be used with caution in the presence of diabetes mellitus, epilepsy, impaired hepatic or renal function, respiratory disorders, cerebral damage, or hypothyroidism. Caution is also advised when giving disulfiram to those who are addicted to other drugs in addition to alcohol. It is probably best avoided in pregnancy.

Disulfiram should not be given until at least 24 hours after the last ingestion of alcohol. Patients beginning therapy should be fully aware of the disulfiram-alcohol reaction and should be warned to avoid alcohol in any form, including alcohol-containing medicines and alcohol-based topical preparations. Reactions to alcohol may occur as long as 2 weeks after the cessation of disulfiram.

The US manufacturers have recommended that regular blood counts and liver function tests should be performed during long-term therapy.

Pregnancy. A report of 2 infants with severe limb-reduction anomalies whose mothers had taken disulfiram during pregnancy.[1] Only 2 similar cases had previously been reported.

1. Nora AH, *et al.* Limb-reduction anomalies in infants born to disulfiram-treated alcoholic mothers. *Lancet* 1977; **ii:** 664.

Interactions

Disulfiram inhibits hepatic enzymes and may interfere with the metabolism of other drugs taken at the same time. It enhances the effects of phenytoin and coumarin anticoagulants and their dosage may need to be reduced. It also inhibits the metabolism and excretion of rifampicin. Toxic reactions have occurred when disulfiram was given with isoniazid or metronidazole. Disulfiram may inhibit the metabolism of paraldehyde leading to an accumulation of acetaldehyde and these drugs should not be used together.

◊ In a study[1] to evaluate the effects of disulfiram on cytochrome P450 isoenzymes, the results suggested that disulfiram-mediated inhibition is mainly selective for CYP2E1 after both acute and chronic dosage.

1. Frye RF, Branch RA. Effect of chronic disulfiram administration on the activities of CYP1A2, CYP2C19, CYP2D6, CYP2E1, and N-acetyltransferase in healthy human subjects. *Br J Clin Pharmacol* 2002; **53:** 155–62.

Analgesics. The potential of disulfiram to impair drug metabolism was shown[1] when it was found to prolong the plasma half-life of *phenazone*, probably by inhibiting the hepatic microsomal mixed function oxidases. It was also suggested[1] that disulfiram alters catecholamine metabolism since urinary excretion of vanilmandelic acid was significantly reduced and that of homovanillic acid was increased.

1. Vesell ES, *et al.* Impairment of drug metabolism by disulfiram in man. *Clin Pharmacol Ther* 1971; **12:** 785–92.

Antidepressants. It has been reported[1] that *amitriptyline* appeared to enhance the disulfiram-alcohol reaction. There is the potential for serious interactions during the disulfiram-alcohol reaction with drugs having CNS actions mediated by noradrenaline or dopamine, such as *tricyclic antidepressants* or those inhibiting the same enzymes as disulfiram, such as *MAOIs*.[2]

1. MacCallum WAG. Drug interactions in alcoholism treatment. *Lancet* 1969; **i:** 313.
2. Sellers EM, *et al.* Drugs to decrease alcohol consumption. *N Engl J Med* 1981; **305:** 1255–62.

Antiprotozoals. For reference to toxicity associated with *metronidazole* given to alcoholic patients who were also receiving disulfiram, see Alcohol, under Interactions of Metronidazole, p.838.

Antipsychotics. It has been suggested[1] that phenothiazine antiemetics such as *chlorpromazine* might increase hypotension because of their α-adrenoceptor blocking activity and should therefore be contra-indicated in patients taking disulfiram. There is the potential for serious interactions during the disulfiram-alcohol reaction with drugs having CNS actions mediated by noradrenaline or dopamine, such as *phenothiazines*.[2]

1. Kwentus J, Major LF. Disulfiram in the treatment of alcoholism: a review. *J Stud Alcohol* 1979; **40:** 428–46.
2. Sellers EM, *et al.* Drugs to decrease alcohol consumption. *N Engl J Med* 1981; **305:** 1255–62.

Benzodiazepines. *Diazepam* was reported[1] to reduce the intensity of the disulfiram-alcohol reaction.

1. MacCallum WAG. Drug interactions in alcoholism treatment. *Lancet* 1969; **i:** 313.

Cannabis. For a suggestion that a combination of disulfiram and *cannabis* may produce a hypomanic state, see p.2275.

Cardiovascular drugs. Clinically serious pharmacodynamic interactions might be anticipated during the disulfiram-alcohol reaction in patients taking other drugs that impair blood pressure regulation, such as *alpha blockers*, *beta blockers*, or *vasodilators*.[1]

1. Sellers EM, *et al.* Drugs to decrease alcohol consumption. *N Engl J Med* 1981; **305:** 1255–62.

Macrolides. Fatal toxic epidermal necrolysis and fulminant hepatitis have been reported[1] after starting *clarithromycin* treatment in a patient who was receiving disulfiram.

1. Masiá M, *et al.* Fulminant hepatitis and fatal toxic epidermal necrolysis (Lyell disease) coincident with clarithromycin administration in an alcoholic patient receiving disulfiram therapy. *Arch Intern Med* 2002; **162:** 474–6.

Pharmacokinetics

Disulfiram is absorbed variably from the gastrointestinal tract and is rapidly reduced to diethyldithiocarbamate (ditiocarb, p.1445), principally by the glutathione reductase system in the erythrocytes; reduction may also occur in the liver. Diethyldithiocarbamate is metabolised in the liver to its glucuronide and methyl ester and to diethylamine, carbon disulfide, and sulfate ions. Metabolites are excreted primarily in the urine; carbon disulfide is exhaled in the breath.

◊ There was marked intersubject variability in plasma concentrations of disulfiram and its metabolites in a study of 15 male alcoholics given single 250-mg doses of disulfiram by mouth and repeated dosing with 250 mg daily for 12 days.[1] Variability might result from the marked lipid solubility of disulfiram, differences in plasma protein binding, or enterohepatic cycling. Average times to reach peak plasma concentrations after single or repeated doses were 8 to 10 hours for disulfiram, diethyldithiocarbamate, diethyldithiocarbamate-methyl ester, and diethylamine, and for carbon disulfide in breath; peak plasma concentrations of carbon disulfide occurred after 5 to 6 hours. Plasma concentrations of disulfiram were negligible within 48 hours of a dose, although concentrations of some metabolites were still raised. In urine, 1.7 and 8.3% of a disulfiram dose was eliminated as diethyldithiocarbamate-glucuronide in the 24 hours after a single and repeated dose respectively, while diethylamine accounted for 1.6 and 5.7%, respectively. In the 24 hours after a single and repeated dose 22.4 and 31.3%, respectively, was eliminated as carbon disulfide in the breath.

1. Faiman MD, *et al.* Elimination kinetics of disulfiram in alcoholics after single and repeated doses. *Clin Pharmacol Ther* 1984; **36:** 520–6.

Uses and Administration

Disulfiram is used as an adjunct in the treatment of chronic alcoholism (see Alcohol Withdrawal and Abstinence, p.1626). Disulfiram is not a cure and the treatment is likely to be of little value unless it is undertaken with the willing cooperation of the patient and is used with supportive psychotherapy.

Disulfiram inhibits aldehyde dehydrogenase, the enzyme responsible for the oxidation of acetaldehyde, a metabolite of alcohol. The resulting accumulation of acetaldehyde in the blood is widely believed to be responsible for many of the unpleasant symptoms of the disulfiram-alcohol reaction which occur when alcohol is taken, even in small quantities, after disulfiram (see Adverse Effects and Treatment, above). Symptoms can arise within 10 minutes of the ingestion of alcohol and last from half an hour in mild cases to several hours in severe cases. It is advisable to carry out the initial treatment in hospital or in a specialised unit where the patient can be kept under close supervision.

Disulfiram is given by mouth. In the UK, the dose is 800 mg, taken as a single dose, on the first day of treatment, reduced by 200 mg daily to a maintenance dose which is usually 100 to 200 mg daily. In the USA, where doses above 500 mg daily are not recommended, an initial dose of 500 mg daily for 1 to 2 weeks is given, followed by a maintenance dose of 250 mg daily or within the range of 125 to 500 mg daily. Treatment should be reviewed after no longer than 6 months. Maintenance therapy with disulfiram may need to be continued for months or years, until the patient is fully recovered socially and a basis for permanent self-control has been established.

A test dose of alcohol has been given under close supervision when the patient is receiving maintenance doses of disulfiram, in order to demonstrate the nature of the disulfiram-alcohol reaction. However, these challenge tests are not routinely recommended, and should not in any case be used in patients over 50 years of age. Many authorities consider that an explicit description of the reaction is sufficient.

Disulfiram implants have been used in an attempt to overcome problems of patient compliance but have been largely abandoned due to lack of clinical efficacy.

Alcoholism. References.

1. Wright C, Moore RD. Disulfiram treatment of alcoholism. *Am J Med* 1990; **88:** 647–55.
2. Hughes JC, Cook CCH. The efficacy of disulfiram: a review of outcome studies. *Addiction* 1997; **92:** 381–95.
3. O'Shea B. Disulfiram revisited. *Hosp Med* 2000; **61:** 849–51.
4. Brewer C, *et al.* Does disulfiram help to prevent relapse in alcohol abuse? *CNS Drugs* 2000; **14:** 329–341.
5. Suh JJ, *et al.* The status of disulfiram: a half of a century later. *J Clin Psychopharmacol* 2006; **26:** 290–302.

Cocaine dependence. Cocaine use may affect the dopaminergic modulation of CNS function; disulfiram is one of several drugs that interact with dopaminergic systems and have been tried in treatment of cocaine abuse and dependence (see Cocaine Withdrawal Syndrome, p.1860).

References.

1. Carroll KM, *et al.* Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry* 2004; **61:** 264–72.

Preparations

BP 2008: Disulfiram Tablets;
USP 31: Disulfiram Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Abstensyl; Vandisul†; ***Austral.:*** Antabuse; ***Austria:*** Antabus; ***Belg.:*** Antabuse; ***Braz.:*** Antietanol; Sarcoton; ***Chile:*** Antabus; Tolerane; ***Cz.:*** Antabus; ***Denm.:*** Antabus; ***Fin.:*** Antabus; ***Fr.:*** Esperal; ***Ger.:*** Antabus; ***Hung.:*** Antaethyl; ***India:*** Esperal; ***Irl.:*** Antabuse; ***Israel:*** Antabuse†; ***Ital.:*** Antabuse; Etiltox; ***Mex.:*** Etabus; ***Neth.:*** Antabus; Refusal; ***Norw.:*** Antabus; ***NZ:*** Antabuse; ***Pol.:*** Anticol; ***Port.:*** Tetradin; ***Rus.:*** Esperal (Эспераль); ***S.Afr.:*** Antabuse; ***Spain:*** Antabus; ***Swed.:*** Antabus; ***Switz.:*** Antabus; ***Thai.:*** Antabuse†; Difiram; ***Turk.:*** Antabus; ***UK:*** Antabuse; ***USA:*** Antabuse.

Multi-ingredient: ***Fr.:*** TTD-B -B ; ***Rus.:*** Lidevine (Лидевин); ***Swed.:*** Tenutex.

Dizocilpine Maleate *(USAN, rINNM)*

Dizocilpine, Maléate de; Dizocilpini Maleas; Maleato de dizocilpina; MK-801. (+)-10,11-Dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]-cyclohepten-5,10-imine maleate.

Дизоцилпина Малеат

$C_{16}H_{15}N,C_4H_4O_4$ = 337.4.

CAS — 77086-21-6 (dizocilpine); 77086-22-7 (dizocilpine maleate).

Profile

Dizocilpine is an antagonist of the excitatory neurotransmitter *N*-methyl-D-aspartate (NMDA). It has been investigated for its antiepileptic properties as well as for a potential role in various other neurological disorders including the prevention of damage due to cerebral ischaemia.

◊ Dizocilpine has good anticonvulsant activity but as it causes alarming psychotropic effects it was abandoned as a possible therapy for epilepsy.[1] Interest in its use as a possible therapy for stroke continued.

1. Richens A. New antiepileptic drugs. *Br J Hosp Med* 1990; **44:** 241.

Dolomite

Profile

Dolomite is a naturally occurring mineral composed of calcium and magnesium carbonate. It has been used as a nutritional supplement but may contain lead and other toxic metals and is not generally recommended.

Preparations

Proprietary Preparations (details are given in Part 3)
Port.: Frutin; ***USA:*** Dolomite.

Multi-ingredient: ***Austral.:*** Prosteo†.

Dong Quai

Angelica Sinensis; Chinese Angelica; Dang Gui; Dang Qui; Danggui.

Pharmacopoeias. In *Chin.*, which specifies the root.
Br. includes separate monographs for Angelica Sinensis Root for use in Traditional Herbal Medicine, and Processed Angelica Sinensis Root for use in Traditional Herbal Medicinal Product.
BP 2008 (Angelica Sinensis Root for use in THM). The dried whole root of *Angelica sinensis* (*A. polymorpha* var. *sinensis*). It contains not less than 0.1% of *Z*-ligustilide ($C_{12}H_{14}O_2$ = 190.2), calculated with reference to the dried material. Protect from moisture.
BP 2008 (Processed Angelica Sinensis Root for use in THMP). The smoked, sliced, and dried root of Angelica Sinensis Root for use in THM. It contains not less than 0.1% of *Z*-ligustilide, calculated with reference to the dried material. Protect from moisture.

Profile

Dong quai is the dried root of Chinese angelica, *Angelica sinensis* (*A. polymorpha* var. *sinensis*) (Apiaceae). It is used in traditional Chinese medicine in the treatment of menstrual and menopausal disorders, respiratory disorders, and herpes zoster infections.

Other *Angelica* spp. employed in herbal medicine are described on p.2258.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Capsella Complex; Dong Quai Complex; Extralife Meno-Care; Feminine Herbal Complex; ***Canad.:*** Natural HRT; ***Hong Kong:*** Phytoestrin†; ***Singapore:*** Phytoestrin.

Drosera

Droséra; Droserae herba; Herba Rorellae; Rorela; Ros Solis; Rossolis; Sonnentau; Sundew.

Profile

Drosera consists of the air-dried entire plant *Drosera rotundifolia* (Droseraceae) and other *Drosera* spp. Preparations of drosera have been used for its reputed value in respiratory disorders.