Review Article

Drug – Alcohol (Ethyl Alcohol) Interactions

S P Dhaneria

Alcohol is the oldest recreational substance, and its consumption is increasing worldwide as it produces a pleasurable effect and allows people to relax and unwind. A large number of over-the-counter and prescription medicine interacts with Alcohol by Pharmacokinetic and/or Pharmacodynamic mechanisms. Alcohol consumption with drugs having CNS depressant properties may lead to marked impairment in psychomotor performance and making the person injury prone. Alcohol consumption increases the systemic toxicity and organ dysfunction caused by certain drugs. Alcohol consumption may cause unpleasant manifestations with a few drugs/substances (didisulfiram-likeeaction). Alcohol may reduce the therapeutic effect of a few drugs. Awareness about the various interactions of alcohol with drugs/medicines/food/herbals/occupational agents will ensure the safety of the people consuming alcohol and may help the physician in clinical decision-making.

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Introduction

Ethyl alcohol is the main constituent of alcoholic beverages. It is a colorless, volatile and inflammable liquid. The term alcohol is used in this text for ethyl alcohol or ethanol. For social and historical reasons, alcohol is usually bought from a store or in a bar or restaurant rather than from a Pharmacy because it is considered to be a drink and not a drug.[1] Consumption of alcohol is on the increase all over the world due to its pleasurable, stress-relieving and blissful effects on the mind/mood (Table 1).

The proof of alcoholic beverage is twice its percentage of alcohol (40% alcohol is 80 proof).

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) formally defines. "At risk" drinking as > 4 drinks per day or > 14 drinks per week for men or > 3 drink per day or > 7 drinks per week for women. A 'drink' is define by CDC as 12 oz of beer, 8 oz of malt liquor, 5 oz of wine or 1.3 oz or a shot of 80-proof distilled spirit or liquor (Table 2).[2]

The ratio between the concentration of alcohol in alveolar air and blood is constant (1: 2100) as per Henry's law (Table 3).[3]

In therapeutics, ethyl alcohol has been used in the management of acute methyl alcohol & ethylene glycol poisoning, injected in closed proximity to nerves and ganglia to relieve pain in neuralgia and inoperable cancers, in sclerotherapy and topically to prevent bed sores.[4]

Alcohol - Drug Interactions

An interaction is said to occur when the effects of one drug are changed by the presence of another drug, food, drink or by some environmental agent.

Alcohol dehydrogenase present in the stomach and liver metabolizes the alcohol. The activity of this enzyme is less in females and therefore, higher blood concentration is achieved in women than men on the consumption of the same amount of alcohol.[5] Acute alcohol ingestion may inhibit the metabolism of various drugs, enhancing their effect. Such drugs include morphine, codeine, phenytoin, tolbutamide, warfarin, benzodiazepimes, and others. Acute alcohol intoxication decreases general anesthetic requirement and elective surgery should be postponed in intoxicated patients. In contrast, chronic alcohol intake may increase the metabolism of various drugs through the induction of metabolizing enzymes, CYP2E1 therefore reducing the effects such drugs like phenytoin, warfarin, propranolol, some benzodiazepines and others.[5] Chronic alcohol drinking increases general anesthetic dose requirement due to Pharmacodynamic cross-tolerance. The hepatotoxic potential of Paracetamol in heavy drinkers is due to the induction of CYP2E1.[5]

Department of Pharmacology, R. D. Gardi Medical College Ujjain, Madhya Pradesh, India.

Correspondence to: S P Dhaneria, Department of Pharmacology, R. D. Gardi Medical College Ujjain, Madhya Pradesh, India. E-mail: drspdhaneria@rediffmail.com

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Table 1: Concentration of alcohol in different alcoholic beverages

Alcoholic Beverages	*Alcohol Concentration*
Light wine	7–9% alcohol
Fortified wine (Sherry, Port)	16–22% alcohol
Effervescent wine	12–16% alcohol
Malted liquors	3–6% alcohol
Spirits (Whisky, Rum, Brandy, Vodka)	40–55% alcohol

Table 2: Corelation of blood alcohol level with behavioral changes

Blood Alcohol level (mg./100 mL)	*Effects observed in human*
< 30	Not noticeable
30–50	Reaction time increased, loss of fine coordination
50–100	Flushing, dilated pupil, euphoria, loss of restraint
100–200	Emotionally unstable, incoordination of thoughts, speech & action, Nystagmus, flushing, dilated & sluggish pupil
200–300	Staggering gait, loss of self-control, marked incoordination of thought, speech & action
300–400	Stupor-dead drunk
400–500	Coma
> 500	Respiratory arrest & death

Table 3: Relationship between liquor consumed and blood Alcohol level[3]

Blood Alcohol Concentration mg%	*Minimum quantity of liquor consumed*		
	Beer (litres)	*Wine (litres)*	*Distilled spirits (mL)*
50	0.8	0.2	70
100	1.6	0.3	130
200	3.2	0.7	275
300	4.8	0.9	410
400	6.4	1.3	550
500	8	1.6	690
600	9.6	1.9	825

1. Drug interactions with alcohol leading to marked CNS depression

Such interactions will cause increased drowsiness, lack of attention, impaired coordination which will make driving the vehicle, handling of machinery and walking downstairs more difficult, accident prone and dangerous. The important interactions are -

- *Interaction with antipsychotic drugs*

Marked sadation is observed with chlorpromazine, flupenthixol, haloperidol, prochlorperazine. Such interaction is less marked with thioridazine and sulpiride. Drinking of Alcohol may increase the risk of extrapyramidal toxicity (Dystonia and Akathisia) due to antipsychotic drugs.[6]

- *Interaction with Antidepressant drugs*

Impaired psychomotor performance is observed on use of amitriptyline, doxepin, imipramine, trazodone, mianserin, maprotiline or mirpazapine in chronic alcoholics. However, such interaction is mild with amoxapine, clomipramine, desipramine and nortriptyline. If atypical antidepressant bupropion is used during abrupt withdrawal of alcohol, the risk of seizures may increase. No significant pharmacokinetic and pharmacodynamic interaction is observed between SSRIs and Alcohol.[1]

- *Interaction with Antiepileptic drugs*

Moderate social drinking (Not more than 3–6 drinks/ week) does not appear to alter plasma concentration of antiepileptic drugs like carbamazepine, phenobarbitone, phenytoin, sodium valproate, ethosuximide and tiagabine. Antiepileptic drugs like carbamazepine, phenobarbitone, primidone, clonazepam, topiramate, and parampanel have sedative action and, therefore, consumption of alcohol may enhance sedation and reduce the ability to perform skilled tasks like driving. Long-term consumption of alcohol by microsomal enzyme induction increases the metabolism of carbamazepine. The risk of seizure will also increase if such person stops taking alcohol (due to increased elimination of Carbamazepine due to relative lack of competing substrate). Chronic heavy drinking increases the metabolism of phenytoin and therefore the dose of phenytoin is to be increased. Moderate to heavy consumption of alcohol may increase risk of seizures within 2 days of last drink.[1]

- *Interaction with Sedative-hypnotic and antianxiety drugs*

CNS depressant effects of barbiturates like phenobarbitone, pentobarbitone, amobarbital, and thiopental sodium are potentiated by moderate to heavy consumption of alcohol. CNS depressant effects of benzodiazepines - chlordiazepoxide, diazepam, lorazepam, alprazolam, clobazam, nitrazepam, midazolam are potentiated by moderate to heavy consumption of alcohol. Anxiolytic effect of lorazepam, and chlordiazapoxide is reduced by alcohol. Increased aggression and anterograde amnesia are reported with flunitrazepam in presence of alcohol.[7] Marked CNS depression is observed with drugs like chloral hydrate, paraldehyde, methocarbamol, meprobamate, buspirone on consumption of alcohol.

Clomethizole is used to manage alcohol withdrawal syndrome due to its sedative, anxiolytic and anticonvulsant properties. Alcohol increases the bioavailability of clomethizole and therefore causes marked CNS depression.[8]

- *Interaction with Opioid Analgesic drugs*

Sedation due to opioid analgesics morphine, pethidine may be potentiated by alcohol intake and such interaction is very significant with dextropropoxyphene. In one out of five deaths due to opioid prescription, alcohol is implicated.[5]

- *Interaction with Anticholinergic drugs*

Marked CNS depression is observed in alcoholics on administration of anticholinergics like atropine, glycopyrronium. There is no pharmacokinetic interaction between scopolamine and alcohol but alcohol consumption is to be avoided in patient on scopolamine therapy due to the risk of drowsiness. However, such risk is less with hyoscine methyl bromide and hyoscine butyl bromide which are quaternary compounds (poor penetration in brain).

- *Interaction with Antihistaminic drugs*

The sedative effect of first-generation Antihistaminics like diphenhydramine, promethazine, hydroxyzine, triprolidine, mebhydrolin, chlorpheniramine, cyproheptadine is enhanced by alcohol consumption. No significant drug interaction of alcohol with second-generation (Non sedative). Antihistaminics like loratadine, desloratadine, fexofenadine, acrivastine and rupatadine when used in their optimum dose range. However, enhanced sedation is observed with cetirizine in alcoholics. Risk of sedation is less when antihistaminic is used as eye drop or nasal spray.[1]

Marked CNS depression is also observed when alcohol is consumed with alpha-blocker indoramine, antiemetic and prokinetic drug metoclopramide (increases the absorption of alcohol) and antianxiety drug buspirone. Occupational agent - Local exposure to DMSO (Diamethyl sulfoxide) at the workplace on consumption of alcohol may increase psychomotor impairment.[1]

2. Alcohol enhancing the toxicity of other drugs

Chronic Alcohol consumption increases the systemic toxicity/organ dysfunction caused by various drugs as under is followed by Table 4.[1,4,5,9,10,17,18]

3. Drugs causing disulfiram like reaction with alcohol

Disulfiram is used in the management of alcohol dependence as aversion therapy. Ethyl alcohol is metabolized to acetaldehyde by alcohol dehydrogenase and then acetaldehyde to acetate by aldehyde dehydrogenase. Disulfiram and citrated calcium carbimide (CCC) block the metabolism of alcohol by inhibiting aldehyde dehydrogenase and therefore causing accumulation of acetaldehyde in body. This accumulated acetaldehyde causes unpleasant manifestations like flushing, nausea, headache, dizziness, breathlessness, palpitation and hypotension. Thus, in presence of disulfiram, if alcohol is consumed, instead of feeling of pleasure, the person experiences the unpleasant manifestations and therefore starts disliking alcohol.[1,4,5]

Following drugs cause disulfiram like reaction (unpleasant manifestation) on intake of alcohol, alcohol containing medication or even topical exposure to alcohol is followed by Table 5.[1,4,5,9,10,17,18]

Anticancer drug - Carmofur is used in the management of pancreatic carcinoma. In such patient to relieve pain

Table 4: Drugs whose toxicity is increased by Alcohol.

Drug	*Risk of ADR increased by alcohol*
Insulin, Sulfonylureas	Hypoglycemia
Metformin	Lactic acidosis
Aspirin	Peptic ulcer and upper GI bleeding (in heavy drinkers)
Paracetamol	Hepatotoxicity (with overdose of Paracetamol)
Nitroglycerin	Dizziness & fainting
INH, Rifampicin	Hepatotoxicity
Cycloserine	Seizures, impaired memory and verbal fluency
Ethionamide	Psychotoxic reaction
Apomorphine	Hypotension
Methotrexate	Hepatotoxicity
Nicotinic Acid	Flushing, pruritus, hepatotoxicity
Leflunamide	Hepatotoxicity
Tacrolimus	Flushing
Dapoxetine, Olanzapine, Quetiapine	Postural hypotension, dizziness
Lithium	Impairment of psychomotor skills
Mefloquine	Psychosis, depression
Ivermectin, Bromocriptine, PDE-5 inhibitors Sildenafil, Tadalafil, Verdenafil (However alcohol may worsen the erectile difficulties)	Postural hypotension
Azathioprine	Hepatotoxicity
Clonidine	Sedation

if alcohol is used to block the coeliac plexus, the patient develops a disulfiram-like reaction.[11]

There are very few reports of disulfiram-like reaction caused by griseofulvin and ketoconazole with alcohol. No clearcut evidence of alcohol causing disulfiram-like reaction with nitrofurantoin.[1,4,5]

- *Alcohol interacting with Occupational agent leading to Alcohol intolerance/disulfiram-like reaction*

Individuals exposed to xylene vapour, trichloroethylene (used in industry as a degreasing agent), dimethyl-formamide or butyraldoxime (present in printing ink) on the consumption of alcoholic beverages may cause alcohol intolerance/disulfiram-like reaction. These reactions seem to be more unpleasant than serious.[1]

- *Alcohol intolerance with edible fungi and herbal medicine*

A disulfiram like reaction is also observed when alcohol is taken after eating the smooth ink(y) cap fungus (*Coprinopsis atramentaria*). No such interaction is observed with fungus lawyers wig (*Coprinus comatus*) and common field mushroom (*Agaricus campestris*).[1]

Daidzin a Chinese herbal medicine also produces disulfiram-like reaction with alcohol and therefore advocated in the management of Alcohol dependence.[10]

- *Treatment of Disulfiram like reaction*

A disulfiram-like reaction is treated with vitamin C. In mild cases (heart rate < 100/min. & general condition good) the vitamin-C (Ascorbic acid) is given in the dose of 1-gm. orally, the satisfactory response is obtained in 30 to 45 minutes. In moderate to severe cases (heart rate 100 - 150/min., BP 150/100 mm of Hg). Ascorbic acid is given in the dose of 1-gm. Intravenously. A satisfactory response is obtained in 3 to 5 minutes. other supportive measures may be needed in critical patients.[12]

Table 5: Drugs causing disulfiram like reaction with alcohol.

Class of drug	*Drugs causing disulfiram like reaction with alcohol*
Cephalosporins (interaction is due to methyltetrazolethiol moiety in the structure of cephalosprorins)	Cefaperazone, cefamandole, cefotetan, ceforanide, moxalactam, cefmetazole
Antibacterial drug	Furazolidone
Antiamoebic drugs Such interaction is not observed with satranidazole	Metronidazole, tinidazole, ornidazole.
Antidiabetic drugs	Sulfonylureas like chlorpropamide, tolbutamide
Alpha blocker	Tolazoline
Anticancer drugs	Procarbazine
Anthelmintic drug	Levamisol
Antiandrogen (used in metastatic prostatic carcinoma, but no disulfiram like reaction is observed with flutamide, bicalutamide)	Nalutamide

4. Drugs whose effect is reduced by alcohol

Chronic alcohol consumption by inducing CYP_3A_4 increases the metabolism of HIV-Protease inhibitors and NNRITs, reducing their anti-HIV response. No significant interaction is observed between Alcohol and Maraviroc.[13] In heavy alcohol drinkers, the plasma concentration of doxycycline is reduced (due to enhanced metabolism) but not of tetracycline. No such interaction is observed in moderate drinking or occasional heavy drinking.[1] Heavy drinking may reduce the therapeutic response of Interferons and increases the risk of Interferon induced hepatotoxicity.[1] Alcohol reduces antidiuretic effect of vasopressin.[4]

5. Alcohol interactions with other substances of abuse

Alcohol is CNS depressant while amphetamine is CNS Stimulant but there is no simple antagonism between these two. But such interaction increasing cardiotoxicity and immune dysfunction is yet to be established. Concurrent use of cannabis and alcohol before driving should be avoided. There is no pharmacokinetic interaction between nicotine and Alcohol however tachycardia is observed on concurrent use. Alcohol increases the plasma concentration of cocaine and its active metabolite, predisposing to risk of IHD and stroke. Caffeine does not counteract the CNS depressant effects of alcohol to a significant level.[2]

6. Food/Vitamin/Herbal - Alcohol interactions

Food and milk reduce the absorption of alcohol, while meal increases the metabolism of alcohol. When alcohol is taken with Serotonin-rich food like bananas, The individual may develop diarrhea, headache and fatigue. A similar problem may be expected with pineapple, kiwi fruit or walnuts.[1]

Consumption of a substantial amount of alcohol may cause vitamin-A deficiency; therefore, vitamin-A supplementation is needed. But on other hand, alcohol potentiates the risk of hepatotoxicity caused by high dose of vitamin-A. Therefore it would be reasonable to control alcohol consumption when vitamin-A is supplemented. In heavy drinkers, inquiry is made about taking non-prescription vitamin preparations, which may contain high doses of vitamin-A.[14]

There is an increase risk of CNS depression and hepatotoxicity on the consumption of kava with alcohol.[1]

certain beers and wines may contain tyramine; therefore, on the administration of non-selective MAO inhibitors, there is a risk of a hypertensive crisis. Tyramine is not present in gin, whisky, vodka and other spirits; therefore, no significant interaction is reported with MAO inhibitors[1]. Penax ginseng (Asian ginseng) increases clearance of alcohol and lower blood alcohol level (due to enhanced metabolism).[15] Liv 52 Ayurvedic herbal drug may reduce hangover effect after alcohol drinking.[16]

7. Cardiovascular drugs – Alcohol interaction

Chronic moderate to heavy drinking raises the blood pressure and therefore reduces the effectiveness of antihypertensive drugs like Beta blockers, ACE inhibitors, diuretics, methyldopa, verapamil to some extent. In such patients, reducing alcohol consumption may reduce dose requirement of antihypertensive drugs. Alcohol may increase the dose requirement of methoxamine. Alcohol may increase the risk of postural hypotension with alpha blockers.[1] Verapamil and cycloserine may increase blood alcohol level.[4]

Other Interactions

No significant drug interaction exists between H_2 blocker or Proton punp inhibitor (PPI) and alcohol. However, drinking could worsen the GI disease for which H_2 blockers/PPI are being given. So restriction of alcohol intake is advice.[1]

Alcohol may cause rapid and potentially harmful release of morphine, hydromorphone, diltiazem, felodipine from their extended/prolonged release formulation (dose dumping effect) and therefore alcohol should be avoided at the time of administration of such drug.[1]

Alcohol increases the concentration of Acitretin - a retinoid used in psoriasis. This drug has teratogenic potential and therefore women of childbearing age is advised not to take alcohol while taking medicine and for at least 2 months after the discontinuation of drug.[1,17]

Metadoxine is known to increase the excretion of alcohol and therefore has been tried in acute alcohol intoxication and for reversing fatty liver changes in chronic alcoholics.[10]

8. Drugs for treatment of Alcohol Dependence

Alcohol dependence is managed in two steps: detoxification and relapse prevention with psychosocial intervention. Detoxification means withdrawal of alcohol with management of withdrawal syndrome. The withdrawal syndrome may be problematic and managed with thiamine, glucose, benzodiazepines (Diazepam to manage delirium and convulsions), carbamazepine (to control seizures) and beta blockers/clonidine (to manage autonomic hyperactivity). Relapse prevention can be achieved by aversion therapy and control of craving for alcohol. The use of disulfiram or CCC may cause disliking for alcohol due to unpleasant manifestations on alcohol consumption. Various drugs have been tried to prevent the craving or intense desire to take alcohol. These drugs are neltrexone, nelmephene (opioid Antagonists), tiapride (D_2 Antagonist), acamprosate (NMDA receptor antagonist), ondansetron (5 HT_3 antagonist), topiramate (Antiepileptic), lithium (Antimanic) and baclofen (GABA mimetic drug).[2,4,5,9,10]

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