RESEARCH ARTICLE

A Study of Cardiovascular Complications of Disulfiram-Ethanol Reaction

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ABSTRACT

Background: Alcohol abuse is a chronic behavioral problem that can further develop as a progressive disease. Disulfiram is the most extensively used deterrent drug for clinical management of alcoholism. A supervised disulfiram-ethanol reaction (DER) test is carried out in patients who are willing for it, and who are skeptical of the effect of disulfiram in causing a DER.

Objective: The aim of this work was to study the possible cardiovascular changes and complications during disulfiram-ethanol reaction in persons fulfilling the inclusion and exclusion criteria.

Materials and Methods: After written informed consent was obtained, 60 subjects underwent alcohol detoxification and received disulfiram 250 mg BD orally for 5 days. On 5th day, alcohol challenge was carried out with constant monitoring of all the vital parameters. Cardiovascular changes were monitored and recorded during the DER.

Results: Disulfiram was generally well tolerated and DER started to occur within 10-15 minutes and lasted for 90-240 minutes. Cardiovascular changes observed were blood pressure changes [hypotension (n=16, 26.67%) and hypertension (n=3, 5%)] and ECG changes [sinus tachycardia (n=22, 36.67%), transient ischemic changes (n=13, 21.67%), occasional atrial ectopics (n=1, 1.67%) and junctional rhythm (n=1, 1.67%)]. Only 23 subjects (38.33%) did not show any significant ECG changes. All subjects recovered with no residual ECG changes except those who developed hypotension (n=16) who required intervention with IV fluids.

Conclusion: Cardiovascular complications can occur even in properly selected subjects having no baseline cardiovascular impairment, which could be serious and potentially life threatening. Based on the results of the present study, disulfiram-ethanol challenge test appears to be a relatively safe procedure if carried out under standardized conditions and using a safe maintenance dose of disulfiram.

KEY WORDS: Disulfiram; Alcohol Abuse; Disulfiram-Ethanol Reaction; ECG Changes

INTRODUCTION

Alcohol abuse is a chronic behavioral problem that can further develop as a progressive disease. The prominent features of alcoholism are characterized by loss of control over the mind and body, poor social life, psychological problems, legal issues, drug-related behavioral problems and deterioration of general health often leading to hospitalization.[1] Alcoholism is increasing worldwide and is becoming a serious concern due to its multifaceted impact. Prevalence of alcohol use disorders is estimated to be around 1.7% of the global population.[2] In India, about 34-42% of adults have reported used alcohol in their lifetime, 5-7% population is estimated to be alcohol abusers and 10-20 million persons are thought to be in need of treatment for alcohol dependence.[3] Alcohol use accounted for 5% of all the risk factors for burden of disease as measured in disability-adjusted life years (DALYs) globally in the year 2004.[4]

Management of alcoholism and its related health problems is complicated and an important therapeutic challenge. Complete abstinence is the ideal therapeutic objective, though it may not always be practical. It can be best achieved by various behavioral approaches and with medications.[5] Drugs can be used to maintain abstinence and prevent relapse. These drugs include deterrent and anticraving drugs. Deterrent drugs help the addict to develop conditioned aversion to alcohol by producing an obnoxious experience and reaction, even if a small amount of alcohol is consumed, thus strengthening his will to abstain from alcohol. Hence, this therapy is also referred as aversion therapy. Deterrent drugs include disulfiram, calcium carbide, citrated calcium carbide and nitrefazole. Anticraving drugs suppress the reinforcing effect of alcohol and decrease the craving thereby helping to maintain a state of abstinence and preventing relapse. Anticraving agents include naltrexone, acamprosate and other drugs such as SSRIs, D_2 antagonists and ondansetron.[6] Among these, disulfiram, naltrexone and acamprosate are the only approved drugs in the management of alcohol abuse.[5]

Disulfiram (Antabuse), chemically diethyl-thiocarbamoyl or tetraethyl thiuram, is the most extensively used deterrent drug for clinical management of alcoholism since its introduction in 1948.[7,8] Disulfiram reacts with the ingested alcohol (disulfiram-ethanol reaction or DER) to promote acetaldehyde accumulation, which is responsible for the unpleasant reaction in alcoholics, thus making them intolerant to alcohol. Accumulation of the toxic metabolite, acetaldehyde, is a result of irreversible inhibition of the enzyme aldehyde dehydrogenase by the metabolites of disulfiram, namely diethyl-thiocarbamate (DTC) and diethylthiomethyl carbamate (DTMC). The effects of disulfiram are seen within 1-2 hours of ingestion, peak action at about 12 hours and effects are sustained up to 72 hours.[5]

DER occurs in subjects maintained on disulfiram therapy, even if they consume a small amount of ethanol (as low as blood alcohol concentration of 5-10 mg/dL).[9] This reaction is produced during alcohol challenge test or if the subject relapses while still on disulfiram therapy (up to 2 weeks after the last dose) in spite of being advised to abstain from alcohol. The reaction is characterized by unpleasant features such as nausea, flushing, vomiting, diarrhea, sweating, cough, throbbing headache, tremor, blurred vision, vertigo, thirst, uneasiness, weakness, confusion, palpitations, hypotension, chest pain and syncope.[6] Severe reactions can be characterized by respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and can rarely lead to death.[10] The intensity of the reaction varies with each individual and is generally proportional to the dose of disulfiram and the ethanol ingested. In chronic alcoholics, acetaldehyde oxidation to acetate may also become impaired. Thus, chronic alcoholics may have a chronically elevated acetaldehyde concentration in the blood, which may result in excessive increase in acetaldehyde level during

the reaction leading to more severe manifestations.[5] DER can begin within 5-15 minutes after ingestion of alcohol and the duration of the reaction can vary from 30-60 minutes to several hours in more severe cases or as long as there is alcohol in the blood.[6]

Disulfiram is used only in selected and well-motivated chronic alcoholics who want to remain in a state of enforced sobriety so that supportive psychotherapeutic treatment can be applied to their best advantage.[11] A supervised DER test is carried out wherever in patients who are willing for it, and who are skeptical of the effect of disulfiram in causing a DER with the consent of the patient and the family. Disulfiram, therefore, is not a cure for alcoholism, but a supportive therapy.[12]

Management of the DER includes supportive measures to restore blood pressure and to treat shock including oxygen, carbogen, intravenous vitamin C and ephedrine sulfate. Antihistamines have also been used intravenously.[13]

Acetaldehyde that is formed during the reaction is highly reactive and can cross link DNA by chemically reacting with nucleic acid bases and may also damage the mitochondria and structural proteins in various tissues. Acetaldehyde is a known myocardial perturbent damaging the myocardial proteins and impairing protein synthesis, thus causing acute and chronic myocardial damage.[14] Acetaldehyde is also implicated in alcoholic cardiomyopathy and acute cardiac failure with cardiac dilatation.[15] In chronic alcoholics, acetaldehyde-induced cardiac damage may remain subclinical and may not be apparent with the routine non-invasive screening procedures like ECG and stress testing, but may be detected by more sensitive non-invasive procedure like echocardiography. Acetaldehyde-induced subclinical myocardial damage in chronic alcoholics, which may not always be revealed during the routine pretest screening procedures, may predispose or contribute to the cardiovascular changes during the reaction.[16]

There have been many reports of cardiovascular complications like cardiac arrhythmias and myocardial ischemic changes seen with DERs.[17-21] However, these findings were based on case reports rather than any systematic studies. There have been no studies reporting cardiovascular changes and complications of DERs in Indian population. Since Indian population is more prone to independently develop cardiovascular diseases, this study was taken up.[16]

The aim of this work was to study the possible cardiovascular changes and complications during DER in persons fulfilling the inclusion and exclusion criteria. The cardiovascular parameters such as pulse, blood pressure and electrocardiogram were assessed and recorded before, during and following the reaction.

MATERIALS AND METHODS

The study was carried out according to the guidelines of Declaration of Helsinki and Good Clinical Practice, at Kempegowda Institute of Medical Sciences and Research Center, Bangalore. The study was reviewed and approved by the Institutional Ethics Committee.

The subjects who met the inclusion and exclusion criteria were informed about the objective, nature, scope and potential benefits/risks of the study. Informed consent was obtained and documented and subject confidentiality was assured. The subjects were made aware of the right to withdraw from the study at any time and no study specific procedures were performed before obtaining the informed consent.

The study was designed to collect data on drug usage and other clinical data from 60 subjects with documented alcohol dependence attending the outpatient psychiatric services. Subjects were recruited from both inpatient and outpatient wards.

Inclusion Criteria

a. Male adult patients aged between 25-45 years
b. Normal baseline biochemical values

Exclusion Criteria

a. Severe physical illnesses
b. Unstable medical conditions
c. Organic brain disorders
d. Neurological diseases or psychiatric disorders
e. Concomitant treatment with other psychotropics, ECT or anticoagulants
f. All other contraindications for disulfiram therapy such as (i) subjects receiving or have recently received alcohol, or alcohol-containing preparations such as cough syrups, elixirs (ii) hypersensitivity to disulfiram or other thiuram derivatives used in the manufacture of items such as pesticides or vulcanized rubber, (iii) concomitant treatment with cefaperazone, chlorpropamide, metronidazole, paraldehyde, nitrofurantoin, griseofulvin, tolbutamide, desipramine, amitriptyline, isoniazid, phenytoin, phenlybutazone, and sulphonylurea class of hypoglycemic agents and (iv) allergy to disulfiram

A detailed general physical and cardiovascular examination was undertaken in subjects who met the inclusion and exclusion criteria. Baseline laboratory investigations included estimation of hemoglobin, TC, DC, ESR, random blood sugar, lipid profile, liver function tests, renal function tests, resting and treadmill ECG.

Study Procedure

The study was conducted in the Department of Psychiatry, KIMS Hospital, Bangalore, which is well equipped with facilities for interventional emergency care, continuous cardiac monitoring and cardiopulmonary resuscitation under the supervision of attending psychiatrist, cardiologist and anesthesiologist.

After undergoing alcohol detoxification, the subjects were administered tablet disulfiram 250 mg twice daily orally for 5 days. On the 5th day, an intravenous infusion of normal saline was maintained with constant monitoring of all the vital parameters immediately prior to the alcohol challenge. Continuous cardiac monitoring was done with a cardiac monitor throughout the alcohol challenge test to record changes in pulse, blood pressure and ECG. A test dose of ethanol (15 ml of 42% v/v whiskey) was given orally in divided doses of 5 ml at 15 minute intervals. If the subjects did not develop any reaction within 15 minutes of the last dose, then further doses of 5 ml were repeated at 15 minute intervals to a maximum of 30 mL. Unpleasant manifestations such as throbbing headache, flushing, nausea, copious vomiting, respiratory difficulty, dyspnea, sweating, palpitation, chest pain, etc., were recorded. Cardiovascular changes during the reaction such as hypotension or hypertension and ECG changes were also recorded.

In those subjects who complained of severe cardiac symptoms such as dyspnea, palpitations, chest pain or in those who developed hypotension or adverse ECG changes, the testing was aborted. The subjects were subsequently stabilized by giving intravenous injection of ascorbic acid 1000 mg and injection hydrocortisone sodium succinate 100 mg (Efcorlin). If these unpleasant symptoms did not subside, the drugs were repeated in the same dose. When the unpleasant cardiovascular symptoms subsided, a repeat ECG was done at the end of one hour. Supportive care given and continuous cardiac monitoring were continued till the subjects completely recovered from the reaction. Once the subjects stabilized, they were shifted to the psychiatric ward with periodic monitoring of all the vital parameters for 8-12 hours.

Statistical Analysis

Safety and efficacy analyses were performed for:

- 'All Subjects Treated Set' (all subjects who took at least one dose of study medication)
- 'Full Analysis Set' (all subjects who took at least one dose of study medication and who had at least one post-baseline assessment of efficacy)

Analysis was carried out according to the intention to treat (ITT) principle. Appropriate

statistical tests were employed to determine if the change in symptoms from baseline were statistically significant ($p<0.05$).

RESULTS

Sixty subjects were enrolled and comprised the all-subjects population. Analysis of demographic characteristics revealed a mean age of 36.2 years (SD±6.74) with a range of 25-45 years. The mean duration of alcohol intake was 12.4 years (SD±6.83) with a range of 2-25 years. The average age of first drink was 23.8 years (SD±5.64) with a range of 13-39 years. A majority of the subjects were also tobacco smokers (61.7%) with duration ranging from 1-30 years.

Disulfiram was generally well tolerated and no adverse effects were reported from any of the subjects. Following the alcohol challenge, reactions started to occur within 10-15 minutes and lasted for 90-240 minutes, with an average duration of 150 minutes. The reactions were characterized by flushing, nausea, vomiting, palpitation, throbbing headache, intense sweating, cough, dyspnea and non-itching erythematous rashes.

Cardiovascular changes observed during the reaction included changes in the pulse rate, blood pressure and ECG. The mean pulse rate increased during the test period and returned to near baseline levels after the conclusion of the test [Table 1]. Both systolic and diastolic changes occurred in blood pressure readings. However, the changes in the diastolic pressures were more prominent and probably may have a predictive value in determining the reaction outcome, although not found statistically significant [Table 2]. In all, 16 subjects developed hypotension (26.67%) and 3 subjects hypertension (5%) with the rest being normal [Table 3]. Analysis of the ECG changes revealed that 22 subjects developed sinus tachycardia (36.67), 13 subjects transient ischemic changes (21.67) and 1 subject each developed occasional atrial ectopics and junctional rhythm (1.67). Only 23 subjects (38.33%) did not show any significant ECG changes [Figure 1].

Within one hour after cessation of the challenge, all subjects recovered with no residual ECG changes except those who developed hypotension (n=16) who required emergency interventional measures with I.V. fluids (normal saline) without needing any vasopressors. Even these subjects reported no adverse sequelae following the reaction.

The post challenge ECG showed completely normal pattern in all subjects without any residual changes indicating that ECG changes observed during the reaction were transient. Among the 22 subjects who developed sinus tachycardia, only 4 showed hypotension and 10 showed transient ischemic changes. During the reaction, 13 subjects developed ischemic changes on the ECG which appeared as ST-segment depression in leads II, III, aVf, V5 & V6 suggesting inferolateral ischemia; ST-segment depression in leads II, III, V5-6 &T wave flattening in lead III suggestive of lateral wall ischemia; and T wave inversion in II, III, aVf indicating inferior wall ischemia. Among 10 subjects who developed sinus tachycardia, 3 developed clinically significant hypotension, 1 subject mild hypertension without sinus tachycardia, and in 8 subjects, blood pressure was within normal limits. There was no correlation between the ischemic changes and duration of alcohol consumption suggesting that the development of the ischemic changes had no relevance to the duration of alcohol consumption.

Table-1: Changes in Pulse Rate*

Pulse rate†	Minimum	Maximum	Mean ± SD	Skewness	
				Std. Error	
Pre Test	50	120	83.45 ± 9.62	0.091	0.309
During Test	82	144	109.63 ± 15.92	0.242	0.309
Post Test	68	100	87.47 ± 7.28	-0.552	0.309

* Beats per minute; † N=60

Table-2: Changes in Blood Pressure*

Changes in BP†		Minimum	Maximum	Mean ± SD	Skewness	
					Std. Error	
Systolic	Pre Test	110	160	131.93 ± 10.42	0.213	0.309
	During Test	70	180	122.27 ± 26.44	-0.133	0.309
	Post Test	100	140	124.00 ± 10.65	-0.148	0.309
Diastolic	Pre Test	70	110	88.00 ± 10.06	-0.043	0.309
	During Test	20	110	74.73 ± 19.69	-0.572	0.309
	Post Test	60	110	83.77 ± 11.13	-0.099	0.309

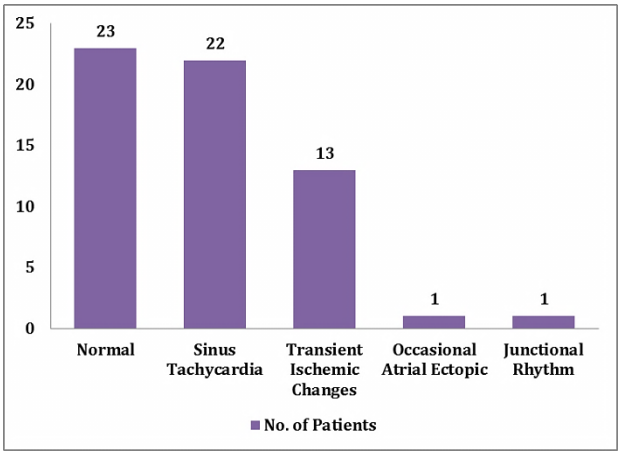
* mmHg; † N=60

Table-3: Blood Pressure Alteration during the Reaction

Blood Pressure changes*	Frequency (%)	Valid	Cumulative Percent
Normal	41 (68.3)	68.3	68.3
Hypotension	16 (26.7)	26.7	95.0
Hypertension	3 (5.0)	5.0	100.0

* N=60

Figure-1: ECG Changes Recorded during Disulfiram-Ethanol Reactions



DISCUSSION

In the present study, cardiovascular effects due to DER were observed and recorded in 60 detoxified and well-motivated subjects fulfilling the inclusion and exclusion criteria.

The cardiovascular changes observed were blood pressure changes (hypotension and hypertension) and ECG changes (sinus tachycardia, transient ischemic changes, occasional atrial ectopics and junctional rhythm). Despite the cardiovascular changes, the subjects remained asymptomatic except for development of palpitations. All subjects reported normal post test systolic and diastolic blood pressures suggesting rapid recovery.

Cardiovascular complications of DER have been documented earlier. The most commonly reported complications were severe hypotension (occasionally hypertension), tachycardia, acute cardiac failure, myocardial infarction and cardiac arrhythmias like atrial fibrillation, atrial flutter and nonsustained ventricular tachycardia. Several deaths have also been reported during the reaction due to myocardial infarction with shock, acute cardiac failure and severe hypotension.[22-26] Most of these fatal reactions were because of either excess disulfiram dosage or because of two or more drinks, but death has also been reported in a subject receiving therapeutic dose of disulfiram after just one drink.[21] Reactions were severe and stormy when higher doses of disulfiram (up to 1-1.5 g/day) were used. In our study, selected subjects were given a maintenance dose of disulfiram 500 mg/day, which is generally accepted as adequate and safe for Indian population.[15]

Hypotension is one of the commonest cardiovascular complications encountered during the DER. This can be explained by the fact that acetaldehyde is also known to release catecholamines from adrenergic nerve terminals and adrenal medulla. This may also contribute to acute cardiovascular complications like tachycardia, hypertension, myocardial ischemia and cardiac arrhythmia during the reaction. However, following continued administration of disulfiram, there may be decreased noradrenaline synthesis due to inhibition of the enzyme dopamine-β-hydroxylase (DBH) by diethylthiocarbamate, resulting in noradrenaline depletion. The direct vasodilator action of acetaldehyde combined with noradrenaline depletion results in hypotension.

Chronic alcoholism is also known to cause

depletion of electrolytes such as potassium and magnesium. Hypokalemia is more common during alcohol withdrawal and acute hypokalemia can cause cardiac arrhythmias.[18,20] Magnesium deficiency may also lead to cardiac arrhythmias.[22]

The cardiovascular manifestations of the DER is the result of the overall consequence of acetaldehyde-induced myocardial depression and vasodilator action, catecholamine release, electrolyte depletion and the nonspecific cardiovascular stress during the reaction. The pattern, extent, severity and duration of the reaction may be variable depending upon the subjects' age, general condition, preexisting cardiovascular status, electrolyte status, the maintenance dose of disulfiram and the amount of alcohol used in the challenge.

In the present study, it is evident that cardiovascular complications can occur even in properly selected subjects having no baseline cardiovascular impairment, which could be serious and potentially life threatening. With higher disulfiram maintenance dose (>500 mg/day), these reactions are likely to be severe, prolonged and stormy. There are no effective rescue measures to cut short or reverse the event though some reports suggest the usefulness of agents such as vitamin C, antihistaminics and hydrocortisone as rescue drugs. However, there is no pharmacological rationale for their use and their efficacy remains to be established.[23]

Based on the results of the present study, disulfiram-ethanol challenge test appears to be a relatively safe procedure if carried out under standardized conditions and using a safe maintenance dose of disulfiram. It may be prudent to employ a more extensive and thorough pretest evaluation of subjects by assessing their electrolyte status (potassium and magnesium) and echocardiography. Biochemical monitoring (plasma acetaldehyde, serum potassium and magnesium) during the reaction may also be useful in the assessment. The procedure should be conducted only by well-trained psychiatrists and physicians who are experienced in handling the possible emergencies and it is very important to advise the subjects against unsupervised medication or self-medication with disulfiram.

CONCLUSION

Cardiovascular complications can occur even in properly selected subjects having no baseline cardiovascular impairment, which could be serious and potentially life threatening. Based on the results of the present study, disulfiram-ethanol challenge test appears to be a relatively safe procedure if carried out under standardized conditions and using a safe maintenance dose of disulfiram.

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