Disulfiram-Induced *De Novo* Convulsions without Alcohol Challenge: Case Series and Review of Literature

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**ABSTRACT**

Seizure induction by disulfiram (DSF) an adverse effect of therapeutic dosages of DSF is less understood. In our prospective case series of eight subjects with alcohol dependence a temporal, dose-dependent, and reversible epileptogenic potential due to DSF was noted. Mean duration of onset of first seizure was 2.13 ± 1.13 weeks after initiation of DSF therapy (125-500 mg/day) with no other detectable causes of seizures. Presence of alcohol withdrawal seizures (50%), DSF-induced hypertension (HTN) (37.5%), psychosis (12.5%) were noted, that may suggest common neurobiological underpinnings like dopamine-beta-hydroxylase inhibition. Various types of DSF-induced generalized seizures (tonic-clonic, 62.5%; myoclonic and tonic-clonic, 25%; myoclonic, 12.5%) were effectively managed by halving initial DSF dose (37.5%) even after cessation of antiepileptics, or stopping DSF (37.5%). Presence of alcohol withdrawal seizures, DSF-induced HTN/psychosis during DSF therapy may be early risk factors for dose-dependent and reversible adverse effect of DSF therapy — seizure induction, emphasizing caution.

**Key words:** Adverse effect, alcoholism, convulsion, disulfiram, hypertension, psychosis, seizure

**INTRODUCTION**

Disulfiram (DSF) is one of the US Food and Drug Administration approved recommended aids in the management of selected cases of alcohol dependence for over six decades, that relies on “psychological threat” to avoid DSF-ethanol reactions. Its toxicity may present different clinical aspects, though the mechanism (direct or idiosyncratic) remains unclear. DSF (125-500 mg/day) related seizures has been documented in very few earlier reports to cause reversible generalized seizures within 2-3 weeks of administration. Surprisingly, most of the related articles were during the period between 1950s and 1980s. This shows the need for research especially, in the Indian context, when alcohol population and wide use of DSF (sometimes surreptitiously) in de-addiction centers are considered. We report prospective series of eight subjects with alcohol dependence that developed *de novo* generalized seizures within 1-6 weeks of DSF therapy without alcohol challenge. A PubMed search was done using the keywords; “disulfiram”, “seizure”, “convulsion”, “epilepsy”, “hypertension” and relevant articles were retrieved supplemented with a manual search of cross references to compile the information on possible mechanisms of DSF-induced seizures.

**CASE REPORT**

Detection of a case with DSF-induced hypertension (HTN) and seizures, led us to monitor blood pressure (BP) in patients on DSF therapy as a matter of therapeutic concern, which revealed a temporal
association of HTN and seizures within 6 weeks of initiation of DSF therapy in three of eight subjects (37.5%) with alcohol dependence. Consecutive cases of alcohol dependence diagnosed as per diagnostic and statistical manual of mental disorders diagnostic criteria,[4] with informed consent for DSF therapy that developed DSF-induced seizures with or without HTN or psychosis were evaluated. BP was recorded manually by sphygmomanometer, with baseline BP defined as that measured after completion of alcohol detoxification, but before initiation of DSF therapy. Severity of HTN was graded as per the European Society of HTN/European Society of Cardiology Guidelines for Management of Arterial HTN.[5] None of the subjects had contraindications for DSF therapy or other comorbid conditions such as psychosis, epilepsy, neuropathies, cirrhosis of liver, head injury, HTN, ischemic heart disease, diabetes mellitus, renal diseases, neurological deficits. Investigations such as complete blood count, blood glucose, electroencephalogram (EEG), electrocardiograph, abdominal ultrasonography, serum electrolytes, liver and renal profiles, cranial magnetic resonance imaging were done to exclude other causes of seizures or HTN.

Compliance with medications was supervised, and abstinence from alcohol was ensured by caregivers. Upon detection of DSF-induced seizures, initial DSF dose was halved (n = 4, 125–250 mg/day) or continued (n = 1, 125 mg/day), and discontinued (n = 3) based on patient preference. Considering the severity of possible DSF-induced seizures, antiepileptics were initiated (n = 7) and discontinued after a period of 1-3 months with no recurrence of seizures, possibly due to halved DSF dose. Table 1 shows the socio-demographic and clinical profile, whereas Table 2 presents the prospective monitoring with management strategies of eight subjects with DSF-induced seizures.

**DISCUSSION**

In our series, the temporal association of DSF initiation and seizure/HTN (1-6 weeks), absence of prior medical history (epilepsy, diabetes, renal illness, or drug intake) contributing to seizure, seizure control with DSF dose-reduction and no recurrence of seizures upon discontinuation of antiepileptics in patients with halved DSF dose, all led to the suspicion of possible association of DSF-induced seizures with HTN and/or psychosis. In our subjects who had fatty liver the dose of DSF was 250-500 mg/day. However, even low-doses of DSF (125 mg/day) in subjects with cirrhosis of liver have been quoted to induce adverse effects due to reduced DSF metabolism.[6] Reduction of dose in three cases showed seizure control with no recurrence even after discontinuation of antiepileptics, possibly suggests dose-dependent epileptogenic adverse effect of DSF. This may imply that DSF-induced seizure can be controlled with antiepileptic drugs, which may be discontinued upon halving or stopping DSF. However, despite low DSF dose (125 mg/day) and valproate (20 mg/kg/day) seizure control was inadequate in one subject, necessitating discontinuation of both drugs with no subsequent recurrence of seizures.

**Table 1: Clinical profile of subjects with disulfiram-induced convulsions (n = 8)**

| Characteristics | Case-1 | Case-2 | Case-3 | Case-4 | Case-5 | Case-6 | Case-7 | Case-8 | Inference |
|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|----------|
| Age (in years)  | 29     | 31     | 34     | 35     | 35     | 36     | 42     | 60     | 37.75±9.76 (mean±SD) |
| DSM-5 diagnosis| ADS+NDS| ADS+NDS| ADS+NDS| ADS+NDS| ADS    | ADS    | ADS+NDS| ADS+NDS| NDS common (5 of 8; 62.5%) |
| Alcohol withdrawal seizures | No | Yes | No | No | Yes | No | Yes | Yes | Present (50%) |
| Baseline SBP and DBP (mm Hg) | 130/80 | 126/80 | 120/80 | 110/74 | 130/80 | 120/70 | 126/78 | 134/80 | 124.5±7.62; 77.5±3.77 |
| Dose of DSF (mg) | 500 | 125 | 250 | 250 | 250 | 500 | 250 | 250 | 296.88±132.58 |
| Onset of convulsions (in weeks) | 3 | 1 | 3 | 1 | 1 | 2 | 4 | 2 | 2.13±1.13 |
| Clinical findings, seizures and number of episodes | GTCS (3); mild hepatomegaly | Recurrent myoclonic seizures of limbs followed by GTCS (2); tongue bite | GTCS (1); no other abnormalities | GTCS (3); no other abnormalities | GTCS (1); mild hepatomegaly; no other abnormalities | Recurrent myoclonic jerks and torticollis; no other abnormalities | Recurrent myoclonic seizures followed by GTCS (2); mild hepatomegaly | GTCS (2) and delirium; vitals stable; mild hepatomegaly | GTCS (62.5%); myoclonic seizures + GTCS (25%); myoclonic seizures (12.5%) |
| Other adverse effects of DSF (in weeks) | Stage-III HTN 170/110 (2); psychosis (3) | Stage-III HTN 170/100 (1) | Nil | Nil | Nil | Nil | Nil | Stage-III HTN 200/110 (4) | DSF-induced HTN (3 of 8; 37.5%) |

*All cases were males with ADS without delirium tremens, †Baseline BP as recorded 12-15 days after admission with DSF initiated 2-4 days before discharge, ‡ESH-ESC guidelines (2013)‡‡, SD – Standard deviation, NDS – Nicotine dependence syndrome, DSF – Disulfiram, HTN – Hypertension, SBP – Systolic blood pressure, DBP – Diastolic blood pressure, GTCS – Generalized tonic-clonic seizures, DSM-5 – Diagnostic and statistical manual of mental disorders, ADS – Alcohol dependence syndrome, BP – Blood pressure, ESH – European Society of Hypertension, ESC – European Society of Cardiology
Disulfiram is relatively nontoxic substance when administered alone that markedly alters the intermediary metabolism of alcohol. Toxic reactions may be delayed until toxic levels of DSF or its metabolites are accumulated in the body due to its delayed elimination from the body.[7] DSF acts by inhibiting aldehyde dehydrogenase, alcohol dehydrogenase and dopamine beta-hydroxylase (DBH).[8] DSF along with its two metabolites, diethyl-dithio-carbamate, and carbon disulfide (CS₂) inhibit DBH activity, a norepinephrine (NE) biosynthetic enzyme, which normally catalyzes the formation of NE from dopamine.[9-13]

Exact mechanism of seizure induction by DSF in humans is less understood. DSF has been found to lower the convulsive threshold and increase the severity and lethality of seizures produced by widely varying mechanisms.[14] First, reduced brain NE and increased brain dopamine (DA) levels due to inhibition of DBH by DSF and its metabolites may lower the seizure threshold without concomitant challenge by alcohol.[15] Second, CS₂, a DSF metabolite and potent neurotoxin may induce convulsions due to acute CS₂ intoxication. Furthermore, chronic exposure to DSF or CS₂ may induce seizures by causing a pyridoxine deficiency possibly resulting in reduced formation of gamma-amino butyric acid, a natural anticonvulsant.[14,16] Third, high concentrations of DSF may inhibit tissue intake of oxygen,[17] leading to tissue hypoxia in the central nervous system which could then result in delirium as well as the associated EEG changes of increased amplitude and slowing of cortical rhythms,[18] which was noted in all of our cases. However, these EEG changes gradually clear with no further occurrence of seizures upon discontinuation of DSF.[19] Occurrence of generalized/myoclonic seizures in alcohol dependent patients can stem from many clinical situations, including head trauma, subdural hematoma, electrolyte disturbances, alcohol-induced exacerbation of chronic seizure disorder, acute alcohol withdrawal states, alcohol-DSF interactions, and so on.[13]

Mechanism of DSF-induced HTN in humans is unclear. We have presented a review on possible mechanisms of DSF-induced HTN in detail elsewhere.[15] DSF impairs the BP regulation by inhibition of the central DBH activity resulting in decreased central NE synthesis, which may interfere with the central alpha-adrenergic activity at the bulbar sympathetic cardio-accelerator, and vasomotor centers, resulting in increased BP.[6] opposite of which is noted with antihypertensive agents like central alpha agonists (clonidine, methyldopa, reserpine, and guanfacine). Considering common underlying possible mechanisms of DSF-induced seizures, HTN and also psychosis (increased DA), we hypothesized these adverse effects to be found in close association. We found DSF-induced HTN (37.5%) and psychosis (12.5%) in subjects with DSF-induced seizures that may suggest common neurobiological underpinnings like central DBH inhibition.

Table 2: Prospective monitoring and management of subjects with disulfiram-induced convulsions (n = 8)

| Characteristics | Case-1 | Case-2 | Case-3 | Case-4 | Case-5 | Case-6 | Case-7 | Case-8 | Inference |
|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|----------|
| EEG             | Abnormal | Abnormal | Abnormal | Abnormal | Abnormal | Abnormal | Abnormal | Abnormal | Abnormal EEG (100%) Abnormal MRI brain (25%)
| MRI brain       | Normal | Cerebral and cerebellar atrophy | Normal | Normal | Normal | Fatty liver Elevation liver enzymes | Fatty liver Elevation liver enzymes | Normal | Abnormal |
| USG abdomen     | Fatty liver | Normal | Abnormal | Normal | Normal | Normal | Normal | Normal | No other contributing causes for epilepsy detected |
| Blood glucose, serum electrolytes, liver and renal profiles | DSF dose reduced (125 mg) and valproate (1000 mg). Later, DSF stopped due to onset of psychosis | DSF dose reduced (125 mg) and valproate (1000 mg for 3 months) | DSF dose reduced (125 mg) and topiramate 100 mg mg for 1 month; well tolerated | DSF dose reduced (125 mg) and topiramate 1000 mg for 1 month | DSF stopped; carbamazepine 600 mg for 1 month | DSF dose reduced (250 mg) and valproate 1000 mg added for 3 months. After stopping valproate, DSF continued at 250 mg with no recurrence of seizures | DSF dose reduced (125 mg) and valproate 1000 mg for 1 month | DSF stopped; no antiepileptics | Effective seizure control by halving (37.5%) or stopping DSF (37.5%) without antiepileptics. One case with 125 mg DSF developed seizures; another psychosis 15.8±9.95 |
| Follow-up period (weeks) | 20 | 17 | 8 | 8 | 4 | 24 | 12 | Effective seizure control by dose reduction (4) or stopping DSF (3) |
| Effect of medical intervention | Abstinence +; no seizures | Abstinence +; no seizures + LF at 17 weeks | Relapse (alcoholic); no seizures after stopping topiramate; LF at 8 weeks | Relapse (alcoholic); no seizures; LF at 8 weeks | Abstinence +; no seizures; LF at 4 weeks | Abstinence +; no seizures | Abstinence +; no seizures; cognitions improved | Effective seizure control by dose reduction (4) or stopping DSF (3) |

DSF – Disulfiram, USG – Ultrasonography (abdomen), EEG – Electroencephalograph, MRI – Magnetic resonance imaging (brain), LF – Lost for follow-up
CONCLUSION

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.[2] Awareness amongst clinicians about DSF-induced seizures/HTN in the holistic management of alcohol dependence appears prudent to prevent misdiagnosis of epilepsy and essential HTN.[3,20] Although DSF-induced seizures are relatively rare, it is clinically significant, potentially serious, dose-dependent and reversible neurotoxic adverse effect of DSF therapy[21] in patients without alcohol challenge.[15] Presence of alcohol withdrawal seizures, DSF-induced — HTN or — psychosis may possibly predict and help to closely monitor such cases in clinical practice, especially in cases with comorbid alcohol and nicotine dependence due to drug level alterations by nicotine through CYP450 enzymes.[3]

Although, appropriate treatment is discontinuation of DSF, halving of DSF dose may appear to be a worthwhile initial option. Antiepileptic agents may be temporarily instituted for the period of time during which the drug is being eliminated from the system.[22] However, DSF may be discontinued if seizures persist even after discontinuation of short-term antiepileptics. Regular monitoring for BP and involuntary jerky movements or unexplained loss of consciousness at least fortnightly for initial 3 months, followed by monthly for next 3 months and later once in 3 months during DSF therapy, may appear prudent to detect the neurotoxic and vascular adverse effect of DSF.[3]

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