Disulfiram-Induced Reversible Hypertension: A Prospective Case Series and Review of The Literature

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ABSTRACT

Disulfiram (DSF) is one of the recommended aids in the management of selected patients with alcohol dependence. Hypertension (HTN) as an adverse effect of DSF therapy is less understood. In our prospective case series of 7 subjects with co-morbid alcohol and nicotine dependence, a temporal, dose-dependent, and reversible grade 1-3 HTN within 1-6 weeks of initiation of DSF therapy (125-500 mg/day) with no other detectable causes of HTN was noted. Challenges and strategies surrounding diagnosis and treatment along with mean change and percentage rise in blood pressure are described. Literature review and clinical description of case series may suggest neurobiological role in its causation. HTN may be a clinically significant, dose-dependent, and reversible adverse effect of DSF therapy, especially in co-morbid alcohol and nicotine-dependent patients. Awareness amongst clinicians may render better health care delivery to subjects with alcohol dependence.

Key words: Adverse effect, alcoholism, disulfiram, hypertension

INTRODUCTION

Disulfiram (DSF) is one of the USFDA-approved recommended aids in the management of selected cases of alcohol dependence for over 6 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 hypertension (HTN) has been documented in very few earlier reports to cause reversible, dose-dependent grade 1-2 HTN within 2-3 weeks of administration, while a systematic review observed no change in blood pressure (BP) with 6 weeks of DSF (250 mg/day) therapy. 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 7 subjects with alcohol dependence that developed reversible grade 1-3 HTN within 1-6 weeks of DSF therapy. A PubMed search was done using the keywords; ‘disulfiram,’ ‘hypertension,’ ‘blood pressure,’ and relevant articles were retrieved supplemented with a manual search of cross-references to compile the information on possible mechanisms of DSF-induced HTN.

CASE REPORT

Detection of a case with DSF-induced HTN led us to monitor BP in patients on DSF therapy as a matter of therapeutic concern, which revealed a temporal association of HTN within 6 weeks of initiation of DSF therapy in another 7 subjects with alcohol...
dependence syndrome diagnosed as per ICD-10 criteria. All had sought inpatient treatment at the Alcohol and Drug De-addiction Clinic, Department of Psychiatry of our Medical Institution. All were males with age range from 31 to 55 years. Six of 7 (85.71%) subjects had uncomplicated alcohol withdrawal state as also co-morbid tobacco dependence syndrome. Only one case had co-morbid diabetes mellitus (with normal BP) since 2 years with euglycemic control on oral hypoglycemic agents. BP was recorded manually by sphygmomanometer, with baseline BP defined as that measured after completion of alcohol detoxification before initiation of DSF therapy. Severity of HTN was graded as per the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines for management of arterial HTN. None of the subjects had high-normal BP or HTN during baseline assessment. DSF was started after written informed consent from patient and spouse/caregiver. The daily dose of DSF ranged from 250-500 mg (mean 428.57 ± 121.99 mg). Compliance with medications was supervised, and abstenance from alcohol was ensured by caregivers. None of the cases had prior medical history of HTN, diabetes, renal problems, neurological deficits, or any drug intake. Family history of alcoholism was noted in 4 subjects and HTN in 2 subjects. Liver function tests revealed marginally elevated liver enzymes. Ultrasonography of abdomen showed mildly enlarged liver with grade-2 fatty infiltration. Renal parameters were within normal limits in all subjects. Upon detection, initial DSF dose was continued in 3 subjects, while dose was reduced (125-250 mg/day) in another 3 subjects based on patient preference and severity of HTN. DSF was discontinued in one subject who had diabetes mellitus with accelerated HTN (200/100 mm Hg), chest pain, and left ventricular strain on electrocardiograph. All subjects were encouraged for life style modifications (LSM) like regular exercises and dietary measures like low salt diet (LSD). Considering the severity of possible DSF-induced HTN, physician initiated anti-hypertensives in 3 subjects. Table 1 shows the socio-demographic and clinical profile, while Table 2 presents the prospective BP monitoring with management strategies of 7 subjects with DSF-induced HTN. Figures 1 and 2 show the changes in systolic

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### Table 1: Socio-demographic and clinical profile of subjects with disulfiram-induced hypertension (N = 7)

| Characteristics | Case-1 | Case-2 | Case-3 | Case-4 | Case-5 | Case-6 | Case-7 | Inference |
|-----------------|--------|--------|--------|--------|--------|--------|--------|-----------|
| Age (in years)* | 31     | 34     | 39     | 40     | 42     | 54     | 55     | 42.14 ± 9.23 (mean ± SD) |
| Alcohol content in volume (g) | 270-300 | 360-540 | 270-360 | 360-540 | 270-360 | 360-540 | 240-270 | 240-540 (mean ± SD) |
| Duration of illness (years) | 10     | 16     | 10     | 20     | 20     | 25     | 25     | 18.0 ± 6.29 (mean ± SD) |
| ICD-10 diagnosis | DT+TDS | ADS+TDS | ADS+TDS | ADS+TDS | ADS | ADS+TDS | ADS+TDS | No co-morbidity (6) |
| Medical co-morbidity | Nil | HTN, CVA (father) | ADS (father, brother) | ADS (brother) | ADS (father) | ADS | DM | Alcoholism common (4) |
| Family history | Nil | HTN (father, brother) | ADS (brother) | ADS (father) | ADS | ADS, DM, HTN (father, brother) | ADS+TDS DM | 126/78 |
| BP on admission (mm Hg) | 150/110 | 146/96 | 140/90 | 140/90 | 140/90 | 160/100 | 126/78 | Alcohol withdrawal HTN 122.0 ± 9.31; 77.43 ± 2.76 |
| BP at discharge (mm Hg) (Baseline) | 130/80 | 110/74 | 120/80 | 110/74 | 124/76 | 134/80 | 126/78 | 428.57 ± 121.99 |
| Dose of DSF (mg) | 500 | 500 | 500 | 250 | 250 | 500 | 250 | 3.29 ± 2.06 |
| Time when HTN first noticed (weeks) | 1 | 2 | 2 | 2 | 6 | 2 | 4 | Usually asymptomatic |
| Clinical features upon rise in BP and maximum rise recorded (mm Hg) | Asymptomatic (170/100) | Asymptomatic (150/110) | Asymptomatic headache, giddiness (170/100) | Asymptomatic headache, giddiness (160/100) | Asymptomatic headache, giddiness (156/100) | Asymptomatic headache, chest pain (200/100) | Asymptomatic headache, chest pain (190/100) | Varying grades 40.08 ± 10.69; 31.22 ± 8.60 |
| Grading of Hypertension | 2 | 2 | 2 | 1 | 1 | 3 | 3 | Reduced (3) |
| Percentage rise in SBP; DBP (in %) | 36.36; 48.64 | 36.36; 48.64 | 41.66; 25 | 45.45; 35.14 | 25.80; 31.58 | 41.79; 25 | 58.73; 28.20 | Continued (4) |
| DSF dose (mg) changes after rise in BP (if any) | 125 | 500 | 250 | 250 | 500 | 125 | 250 | |

* All cases were males with alcohol dependence syndrome (ADS). † Ethanol in grams = Amount of alcohol consumed × 0.8 × Alcohol content in percentage/100; ‡ All other 6 cases had uncomplicated alcohol withdrawal state; except one case of delirium tremens (DT); † † Baseline blood pressure (BP) as recorded 12-15 days after admission with disulfiram initiated 2-4 days before discharge; † † † ESH-ESC Guidelines (2013); TDS – Tobacco dependence syndrome; DSF – Disulfiram; DM – Diabetes mellitus; HTN – Hypertension; CVA – Cerebrovascular accident (hemorrhagic stroke); SBP – Systolic blood pressure; DBP – Diastolic blood pressure.
Table 2: Prospective monitoring of blood pressure and management of subjects with disulfiram — induced hypertension (N = 7)

| Characteristics                  | Case-1 | Case-2 | Case-3 | Case-4 | Case-5 | Case-6 | Case-7 | Inference         |
|----------------------------------|--------|--------|--------|--------|--------|--------|--------|------------------|
| Changes in BP during follow-up   |        |        |        |        |        |        |        | 48.86 ± 13.70 mm of Hg |
| Week-1                           | 170/100| 110/74 | 120/80 | 110/74 | —      | —      | —      | (mean SBP rise)   |
| Week-2                           | 140/90 | 150/110| 140/90 | —      | 156/100| 190/100| —      | 24.0 ± 5.77 mm of Hg |
| Week-3                           | —      | 170/100| —      | 130/88 | —      | 140/90 | —      | (mean DBP rise)   |
| Week-4                           | —      | 140/90 | —      | 90/60  | 120/86 | —      | 130/70 | —                |
| Week-5                           | —      | —      | —      | —      | —      | —      | —      | Alcoholic-induced liver damage |
| Week-6                           | —      | —      | —      | —      | —      | —      | —      | common (fatty liver) |
| Week-8                           | —      | —      | —      | —      | —      | —      | —      | —                |
| Investigations                   | USG: Fatty liver; Normal liver and renal profiles. | Mild elevation of liver enzymes; Normal renal profile. | Mild elevation of liver enzymes; USG: Fatty liver. Normal renal profile. | Mild elevation of liver enzymes; Normal renal profile. | Mild elevation of liver enzymes; USG: Fatty liver; Normal renal profile. | Mild elevation of liver enzymes; USG: Fatty liver; Normal renal profile. | Mild elevation of liver enzymes; USG: Fatty liver; Normal renal profile. | Alcoholic-induced liver damage |
| Medical management of DSF-induced HTN | DSF dose reduced LSM + LSD | DSF continued LSM + LSD | DSF dose reduced LSM + LSD | DSF continued LSM + LSD | DSF dose reduced LSM + LSD | DSF continued LSM + LSD | DSF continued LSM + LSD | Anti-hypertensives (Metoprolol 50 mg). BP controlled. DSF continued. |
| Effect of medical intervention on BP | 120/84 | 130/84 | 130/80 | 120/82 | LF     | 130/80 | 120/80 | Effective control |
| Follow-up after DSF discontinuation | Alcohol use | Abstinence | Abstinence | Alcohol use | Relapse | Abstinence (DSF continued) | Abstinence | None had essential HTN after withdrawal of DSF. |
| Week-12                          | 110/70 | 110/70 | 130/70 | 124/80 | LF     | 130/74 | 110/70 | —                |
| Week-24                          | LF     | 116/84 | 110/70 | 116/70 | LF     | 134/80 | 124/80 | —                |
| Week-52                          | LF     | LF     | 120/80 | LF     | LF     | LF     | 130/70 | —                |
| Reversibility to normal BP       | Reversible | Reversible | Reversible | Reversible | -      | Controlled with anti-hypertensives | Reversible | Reversible |

DSF – Disulfiram; BP – Blood pressure (mm of Hg); SBP – Systolic blood pressure; DBP – Diastolic blood pressure; ECG – Electrocardiogram; HTZ – Hydrochlorothiazide; LF – Lost for follow-up; LSM – Life style modifications; LSD – Low salt diet; USG – Ultrasoundography (of abdomen); FBS – Fasting blood sugar; PPBS – Post-prandial blood sugar

BP (SBP) and diastolic BP (DBP) from baseline, respectively, in our series.

**DISCUSSION**

DSF is relatively non-toxic substance when administered alone that markedly alters the intermediary metabolism of alcohol. It acts by inhibiting aldehyde dehydrogenase, alcohol dehydrogenase, and dopamine beta-hydroxylase (DBH).\[11\] DSF along with its two metabolites, diethyldithiocarbamate, and carbon disulphide inhibit DBH activity, a norepinephrine (NE) biosynthetic enzyme, which normally catalyzes the formation of NE from dopamine.\[12\] This increases urinary excretion of the main dopamine metabolite homovanillic acid and decreases urinary excretion of NE and its major metabolite vanillylmandelic acid.\[7\] Furthermore, side-effects of DSF such as fatigue, tremor, reduced sexual potency, headache, and dizziness can be mediated by sympathetic nervous system where NE is the neurotransmitter.\[13\]

Mechanism of DSF-induced HTN in humans is unclear. Central nervous system alpha-adrenergic receptors modulate peripheral autonomic activities both, which regulate BP.\[7\] Possibly, changes in central or peripheral NE activity are responsible for the increase in BP.
Peripheral synthesis of NE is probably not affected by the DSF as it is noted to have no effect on the pressor effect of tyramine and NE,[7] as also plasma levels of NE increase following long-term high-dose (> 500 mg/day) DSF therapy.[5] DSF limits NE synthesis in sympathetic nerves but not in the adrenal medulla, possibly due to large reserve of DBH in adrenals rendering DSF incapable of making DBH activity rate limiting and also due to limited access of drug to the adrenal DBH.[7] As DBH enzyme doesn’t cross the blood brain barrier and DSF does not inhibit plasma DBH levels, there remains possibility of central inhibition of DBH in brain and possibly deplete brain NE levels, thereby increase in BP.[6] Thus, it might be speculated that reduced DBH activity, due to either genetic factors or to effects of DSF, might reduce NE concentrations in critical areas of the brain and thereby increase BP.[7] DSF also inhibits uptake of monoamines by chromaffin granules,[14] which may result in increased amounts of catecholamine reaching the plasma. However, DSF increases the nitroglycerine-induced postural hypotension while decreasing the accompanying tachycardia.[7] This implies that DSF impairs the BP regulation through central nervous system 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.[4] opposite of which is noted with anti-hypertensives like central alpha agonists (clonidine, methyldopa, reserpine, and guanfacine).

In a small, randomized, double-blind, placebo-controlled trial on DSF therapy (250 mg/day), a significant increase in SBP with mean change in BP of 8.35 ± 1.3 mm Hg (P < 0.001) in those on DSF therapy was noted, although discontinuation of DSF was not advised.[6] However, in our study, mean rise in SBP was 48.86 ± 13.7 mm Hg and that of DBP was 24.0 ± 5.77 mm Hg with mean duration of its detection being 3.29 ± 2.06 weeks. This may be due to usage of relatively higher DSF dose (428.57 ± 121.99 mg) in our sample or due to comorbid nicotine dependence (85.71%) as nicotine may alter blood levels of DSF through cytochrome P450 enzyme inhibition.[3,11] Mean percentage change in BP from baseline of 40.08 ± 10.69% rise in SBP and 31.22 ± 8.60% rise in DBP in our series may implicate the severity of this adverse effect in patients on DSF therapy. Paradoxically, DSF-ethanol reaction may produce a hypertensive therapy, all led to the suspicion of possible DSF-induced HTN. 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 HTN due to reduced DSF metabolism.[4] Reduction of dose in 3 cases showed mild reduction in BP, although LSM and LSD helped in 2 cases possibly suggests dose-dependent vascular adverse effect of DSF with some beneficial effect of LSM/LSD. In 3 subjects managed with anti-hypertensives, 2 cases showed a significant fall in BP upon discontinuation of DSF necessitating discontinuation of anti-hypertensives with subsequent return to normal BP; while another case showed an adequate control of HTN upon anti-hypertensives being continued with reduced DSF dose (125 mg/day). This may imply that DSF-induced HTN can be controlled with anti-hypertensive agents, which needs to be discontinued upon stopping DSF.

In our series, the temporal association of DSF initiation and HTN (1-6 weeks), absence of prior history of HTN, diabetes, renal illness or drug intake suggestive or contributing to HTN, reduction in BP with DSF dose-reduction, and appearance of hypotension upon discontinuation of DSF during anti-hypertensive

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**Figure 1:** Changes in systolic blood pressure from baseline during disulfiram (DSF) therapy (N = 7)

**Figure 2:** Changes in diastolic blood pressure from baseline during disulfiram (DSF) therapy (N = 7)
reaction in some cases. However, this was not the case in our patients whose compliance was ensured by supervised medication as also the findings of temporal causation of side-effect, gradual persistent increase in BP, and a dose-dependent reduction in the BP with a return to normal values following the discontinuation of DSF and/or anti-hypertensives may support it to be drug-related HTN. These findings reflect DSF-induced HTN as a significant vascular adverse effect that needs early detection and management.

CONCLUSION

DSF 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. HTN may be a clinically significant, dose-dependent, and usually reversible adverse effect of DSF therapy. Its awareness amongst physicians and psychiatrists in the holistic management of alcohol-dependent patients is worthwhile to keep a follow-up and sustain patient compliance with the drug, as also prevent misdiagnosis of essential HTN. In our opinion, an index of suspicion for DSF-induced HTN is needed, especially in cases with co-morbid alcohol and tobacco dependence. In detected individuals, reduction of DSF dose may be advised along with LSM, LSD, and anti-hypertensives. However, DSF may be discontinued if significant HTN persists. Regular BP monitoring for 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 ‘silent’ neurovascular adverse effect of DSF.

REFERENCES

1. Suh JJ, Pettinati HM, Kampman KM, O’Brien CP. The status of disulfiram: A half of a century later. J Clin Psychopharmacol 2006;26:290-302.
2. Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. Drug Saf 1999;20:427-35.
3. Kulkarni RR, Bairy BK. Disulfiram induced reversible hypertension: A prospective case study and brief review. Indian J Psychiat Med 2013;35:217-9.
4. Volcer L, Nelson KL. Development of reversible hypertension during disulfiram therapy. Arch Intern Med 1984;144:1294-6.
5. Lake CR, Major LF, Ziegler MG, Kopin IJ. Increased sympathetic nervous system activity in alcoholic patients treated with disulfiram. Am J Psychiatry 1977;134:1411-4.
6. Silver DF, Erwing JA, Rouse BA, Mueller RA. Responses to disulfiram in healthy young men: A double-blind study. J Stud Alcohol 1979;40:1003-13.
7. Rogers WK, Benowitz NL, Wilson KM, Abbott JA. Effect of disulfiram on adrenergic function. Clin Pharmacol Ther 1979;25:469-77.
8. Peachey JE, Brien JF, Roach CA, Loomis CW. A comparative review of the pharmacological and toxicological properties of disulfiram and calcium carbimide. J Clin Psychopharmacol 1981;1:21-6.
9. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. 10th ed. Geneva: World Health Organization; 1992.
10. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281-357.
11. Disulfiram. Available from: http://www.pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?q=all&cid=3117#ec. [Last Accessed on 2012 Dec 9].
12. Weinshenker D, Schroeder JP. There and back again: A tale of norepinephrine and drug addiction. Neuropsychopharmacology 2007;32:1433-51.
13. Ritchie JM. The aliphatic alcohols. In: Goodman LS, Gilman A, editors. The Pharmacological Basis of Therapeutics. 5th ed. New York: MacMillan Publishing Co.; 1970. p. 137-51.
14. Schlichter D, DaPrada M, Pletscher A. Interference of inhibitors of dopamine-β-hydroxylase with uptake of monoamines by chromaffin granular membranes. Eur J Pharmacol 1975;34:223-7.
15. Zapata E, Orwin A. Severe hypertension and bronchospasm during disulfiram-ethanol test reaction. BMJ 1992;305:870.
16. Huffman JC, Stern TA. Disulfiram use in an elderly man with alcoholism and heart disease: A discussion. Prim Care Companion J Clin Psychiatry 2003;5:41-4.
17. Grover S, Bhatija G, Basu D. Pharmacoprophylaxis of alcohol dependence: Review and update Part 1: Pharmacology. Indian J Psychiatry 2007;49:19-25.
18. Srinivasan TN, Suresh TR, Vasantha J. Adverse effects of disulfiram and calcium carbimide. J Clin Psychopharmacol 1979;25:469-77.