Case Report

Disulfiram Induced Reversible Hypertension: A Prospective Case Study and Brief Review

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ABSTRACT

Disulfiram (DSF) is one of the recommended aids in the management of alcohol dependence. Hypertension may be a clinically significant, dose-dependent, and usually reversible adverse event of DSF therapy. We report 6 month prospective study of normotensive case of comorbid alcohol and tobacco dependence that developed reversible stage-II hypertension within 2-4 weeks of DSF therapy. We suggest that regular monitoring of blood pressure at least fortnightly for 1st 3 months, followed by monthly for next 3 months, and later once in 3 months, may possibly detect “silent” adverse event of DSF – hypertension.

Key words: Adverse event, alcohol dependence, disulfiram, hypertension

INTRODUCTION

Disulfiram (DSF) is one of the recommended aids in the management of selected cases of alcohol dependence. Drug and alcohol de-addiction/rehabilitation centers utilize DSF in selected patients, sometimes surreptitiously, as an alcohol deterring agent. For more than 55 years, DSF has been approved by the USFDA for the treatment of alcohol dependence. It is a unique medication that relies on “psychological threat” to avoid DSF-ethanol reactions. [1] DSF toxicity may present the different clinical aspects, though the mechanism of toxicity (direct or idiosyncratic) remains unclear. [2] DSF (125-500 mg/day) related hypertension has been documented in very few earlier reports to cause reversible, dose-dependent stage-I and stage-II hypertension within 2-3 weeks of administration,[3-6] while a systematic review observed no change in blood pressure (BP) with 6 weeks of DSF (250 mg/day) therapy.[7] 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 its wide use in de-addiction centers are considered. We report a 6 month prospective study of a normotensive case with the comorbid alcohol and tobacco dependence that developed hypertension in temporal association to DSF administration that showed a dose-dependent reduction and reversal to normal BP on discontinuation of DSF. A brief review of relevant literature has been undertaken to compile information on possible mechanism of DSF induced hypertension. A PubMed search was carried out using the keywords; “disulfiram,” “hypertension,” “blood pressure,” and relevant articles were retrieved supplemented with a manual search of the cross references.

CASE REPORT

A 39-year-old married adult male, from urban and middle socio-economic background, presented with a history of daily alcohol consumption (92-123 g of
ethanol/day) and chewing of tobacco (15-20 packets) since 10 years with the dependence pattern since 4 years. He was diagnosed as alcohol dependence syndrome, and tobacco dependence syndrome in uncomplicated withdrawal state as per ICD-10 diagnostic criteria.[8] He had no prior medical history of hypertension, diabetes, heavy metal exposure, epilepsy, neurological deficits, or any drug intake. Family history of alcoholism, but not hypertension was noted in his father and brother.

On admission, vital parameters showed marginal alcohol withdrawal sympathetic activity with pulse rate of 96 beats/min and BP of 140/90 mm of Hg. His general physical and the systemic examination revealed no other abnormal findings, except for fine tremors of both hands and mild hepatomegaly. Patient had pre-occupations with alcohol, anxious mood with preserved cognitions, and grade-4 insight. After alcohol detoxification, his BP had stabilized to 120/84 mm of Hg on day-8 of admission. Electrocardiograph revealed no abnormalities. Hematological and biochemical investigations such as complete blood count, blood glucose (105 mg/dl), blood urea (25 mg/dl), and serum creatinine (1.0 mg/dl) were within normal limits. Liver function tests were normal except for elevated liver enzymes (gamma-glutamyl transferase 96 units/L; serum glutamic oxaloacetic transaminase 120 units/L; serum glutamic pyruvic transaminase 56 units/L). His ultrasound abdomen showed mildly enlarged liver with grade-2 fatty infiltration. Considering frequent relapses, patient, and spouse were explained about the nature of illness, and its various treatment modalities available including DSF. Written informed consent for DSF therapy was taken and a dose of 500 mg/day was initiated. Patient was discharged with DSF (500 mg/day), and multi-vitamin supplementation. At discharge, his vital parameters were stable with pulse of 86 beats/min, and BP of 130/80 mm of Hg.

Compliance with medications was ensured and supervised by his spouse. A fortnight later, patient complained of gradual onset occipital headache and giddiness with pulse rate of 86 bpm and BP of 146/100 mm of Hg. Life style modifications and dietary measures along with above prescribed medications were advised. On week-4 of DSF therapy, his complaints of headache, giddiness worsened, and BP increased to 170/110 mm of Hg. In view of recent inclusion of DSF, with the absence of prior medical illnesses or drug history contributing to hypertension, possibility of drug induced (DSF) hypertension was suspected. Subsequently, DSF was reduced to 250 mg/day and BP reduced to 150/96 mm of Hg a week later. DSF was further reduced to 125 mg/day following this observation and antihypertensive agents such as telmisartan 40 mg and hydrochlorothiazide 12.5 mg/day were also initiated on the physician’s advice. A month later (week-8), patient reported with increased giddiness and physical fatigue with BP of 90/60 mm of Hg despite abstinence. Anti-hypertensive agents were withdrawn and DSF was discontinued completely. Fortnight later (week-10), patient had reached his premorbid levels of BP to 110/70 mm of Hg. Psycho education about medical illness, life style modifications such as regular exercises and dietary measures were advised. Six months later, patient had maintained complete abstinence from alcohol as well as tobacco, and his BP was 130/80 mm of Hg [Figure 1].

DISCUSSION

DSF, an alcohol deterring agent that is relatively nontoxic substance when administered alone, markedly alters the intermediary metabolism of alcohol. It acts by inhibiting aldehyde dehydrogenase, alcohol dehydrogenase and dopamine beta-hydroxylase (DBH).[9] 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.[10] This increases urinary excretion of the main dopamine metabolite homovanillic acid and decreases urinary excretion of NE and its major metabolite vanillylmandelic acid.[6] 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.[11]

Central nervous system alpha adrenergic receptors modulate peripheral autonomic activities both, which regulate BP.[6] Possibly, changes in central or peripheral NE activity are responsible for the increase

![Figure 1: Systolic and diastolic blood pressure variations in an abstinent patient diagnosed with alcohol dependence on disulfiram (DSF) therapy (HTZ-hydrochlorothiazide)](image)
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, as also plasma levels of NE increase following long-term high-dose (>500 mg/day) DSF therapy. However, DSF increases the nitro-glycerine induced postural hypotension while decreasing the accompanying tachycardia. 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, opposite of which is noted with antihypertensive agents like central alpha agonists (clonidine, methyldopa, reserpine, and guanfacine).

DSF has an inhibitory effect on certain cytochrome P450 (2E1, 2C9, 3A4, 3A5) enzymes. Nicotine also has an inhibitory effect on many cytochrome P450 enzymes (1A1, 1A2, 2A6, 2A13, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4). Comorbid tobacco dependence in patients on DSF therapy may have a role in drug level alteration as both share common P450 enzymes (1A1, 1A2, 2A6, 2A13, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4). Paradoxically, ethanol-DSF reaction may produce a hypertensive reaction in some cases. This was not the case in our patient whose abstinence and compliance was ensured by supervised medication as also the finding of temporal association of side-effect, gradual persistent increase in BP over time and a dose-dependent reduction in the BP with a return to normal values following the discontinuation of DSF may reflect it to be drug related hypertension.

An awareness of the adverse effect is useful to keep a follow-up and sustain patient compliance with the drug. Hypertension may be a clinically significant, dose-dependent and usually reversible side-effect of DSF therapy. In our opinion, an index of suspicion for vascular side-effects of DSF in cases with the comorbid alcohol and tobacco dependence may detect and also prevent misdiagnosis of essential hypertension. We suggest that in detected individuals, reduction of dose may be advised along with life style modification, dietary measures, and regular monitoring of BP. However, DSF may be discontinued if significant hypertension persists. Regular monitoring of BP at least fortnightly for 1st 3 months, followed by monthly for next 3 months, and later once in 3 months, may possibly detect “silent” adverse event of DSF – hypertension.

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