

Syncope following sofosbuvir therapy for chronic hepatitis c: a report of two cases

Abstract

The recently approved direct acting antiviral drug, Sofosbuvir,¹ represents a revolution in treatment of chronic hepatitis C infection. Little is known about its long term side effects. Recent reports had drawn the attention to the possible cardio-toxic effect of sofosbuvir when combined with amiodarone. In our cases we reported occurrence of syncopal attacks in two cases few days after administration of sofosbuvir. Syncope was triggered by suddenly standing up from sitting position in one patient and by micturition in the other. We suggest the occurrence of autonomic disturbance following sofosbuvir intake, an observation which need further post marketing evaluation in a large number of cases to clarify the cardio-autonomic effects of sofosbuvir.

Keywords: sofosbuvir, amiodarone, hepatitis c virus, ledipasvir, vasovagal

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Abbreviations: BP, blood pressure; OH, orthostatic hypotension

Introduction

Recently, sofosbuvir an oral nucleotide polymerase inhibitor has been approved as a treatment for hepatitis C virus in combination with ribavirin/interferon for 12weeks¹ or interferon free regimens with ribavirin for 24weeks.² Little is known about the side effects of sofosbuvir. In clinical studies, fatigue and headache were more common in patients treated with sofosbuvir and ledipasvir compared to placebo. When sofosbuvir and ledipasvir were administered with interferon/ ribavirin, the most frequent adverse drug reactions were consistent with the known safety profile of interferon and ribavirin.³ Also, serious slowing of the heart rate can occur when the anti arrhythmic drug amiodarone is taken together with either ledipasvir and/sofosbuvir.⁴ Syncope is a transient and abrupt loss of consciousness with loss of postural tone due to transient global cerebral hypo perfusion characterized by rapid onset, short duration, and spontaneous complete return to preexisting neurologic function. Syncope could be reflex (e.g. Vasovagal, Situational, Carotid sinus), cardiac or orthostatic.⁵ A sudden cessation of cerebral blood flow for as short as 6-8 has been shown to be sufficient to lead to complete loss of consciousness.⁶ Seizures, metabolic and psychic disorders have to be differentiated from syncope due to similar presentations.⁵ Here, we describe two cases of syncope following sofosbuvir combination therapy for CHC.

Case 1

A 61years male patient was diagnosed as chronic hepatitis C with hepatic fibrosis stage F4 by Fibro scan, normal complete blood picture and Child-Pugh class A/5. There was no history of cardiovascular disease, hypertension, diabetes mellitus or seizures or any other regular medication use. His weight was 87Kg. the patient started sofosbuvir 400mg/day plus ribavirin 1000mg/day for 24weeks. His blood picture on week 1 and 2 after starting treatment was normal. On the day 21 of treatment, the patient had a syncopal attack immediately after getting out of his car. The attack occurred suddenly with no evident

prodromal symptoms, lasted for about 20seconds and then recovered spontaneously. He was transferred to the hospital, on admission, his sitting blood pressure (BP) was 132/80mmHg and had dropped to 87/60mmHg immediately after standing, pulse was 87 BPM regular, Head and neck, cardiac, chest and abdominal examination were free, neurological examination was free. Random blood glucose was 149mg/dl, Hb was 13.6g/dl; Twelve lead ECG revealed normal sinus rhythm with no intra-ventricular conduction disturbance, and echocardiography excluded any structural cardiac abnormalities. Twenty-four hour Holter monitoring revealed no arrhythmias. Orthostatic hypotension (OH) was the presumed diagnosis, sufficient water intake as well as fludrocortisone 0.2mg/day were prescribed and close follow up was planned.

Case 2

A 44years male patient with chronic hepatitis C was assigned for triple therapy of interferon 180µg/week, ribavirin 1000mg/day and sofosbuvir 400mg/day for 12weeks. No history of diabetes mellitus, hypertension cardiac or chest diseases or regular daily medication use. Pre-treatment data were normal for clinical examination and investigations showed Child-Pugh class A/5, METAVIR A3F2, normal blood picture and thyroid profile. On the 9th day of treatment, the patient had an attack of syncope immediately after micturition. The patient lost his consciousness and his postural tone for few seconds and then came back again spontaneously as witnessed. On the next day, the patient came to the clinic for assessment. Clinically, he was free, pulse was 72 BPM regular, BP was 128/84mmHg on lying flat and 113/79mmHg immediately on standing, FBS was 97mg/dl, Hb was 12.3g/dl, total cholesterol was 143mg/dl. His 12-lead ECG revealed normal sinus rhythm with no evidence of intra-ventricular conduction abnormalities, transthoracic echocardiography revealed no structural heart defects. Computed tomography was normal. Situational syncope was diagnosed. The patient was given detailed advise on what should he do to avoid recurrence of syncope in addition to proper fluid intake.

Discussion

An orthostatic syncope result from autonomic nervous failure with

the sympathetic efferent activity is impaired so that vasoconstriction is deficient and upon standing, BP falls and syncope or pre-syncope occurs. Initial OH is characterized by a BP decrease immediately on standing of >20mmHg in systolic or 10mmHg in diastolic BP, then rapidly returns to normal, so the period of hypotension and symptoms is short.⁷ The mismatch between cardiac output and peripheral resistance (PR) has been the established mechanism.⁸ The initial response to standing includes two phases of increased HR. The *immediate phase* (within 3seconds), due to abrupt inhibition of cardiac vagal activity^{9,10} through motor signals from higher brain centers that stimulate the cardiovascular centers,¹¹ as well as feedback reflex from muscles mechanoreceptors (muscle-heart reflex) and the *delayed phase* (peak after ~12s) which results from inhibition of cardiac vagal signals and an increase in sympathetic stimulation to the heart (arterial baroreflex compensation).^{9,12} Previous reports showed that cardiopulmonary receptor reflex, rather than muscle pump or peripheral vasodilatation, is the main participant in the maintenance of PR, which we supposed to be impaired in our case number 1.⁷

Situational syncope; a subtype of reflex (neurally-mediated) syncope, occurs with specific circumstances. Post-exercise, post micturition, cough-producing syncope and postprandial syncope may occur in middle-aged and elderly persons representing an early manifestation of autonomic failure to activate compensatory reflexes before they experience typical OH. Vasodilation, bradycardia and systemic hypotension occur as a reflex leading to decreased cerebral blood flow.¹³ Alterations in autonomic activation are responsible for reflex syncope; these include a *Cardio-inhibitory response*, with high parasympathetic activation leading to sinus bradycardia or variable degrees of atrio-ventricular block; *A vasodepressor response*, due to inhibition of sympathetic activity leading to hypotension and *A mixed response*.¹⁴

Syncope following sofosbuvir therapy has been recently described by Renard S et al.¹⁵ in three cases reports with exacerbation of pulmonary hypertension presented by syncope. They claimed that antiviral therapy may reduce the vasodilator inflammatory mediators which led to increase in pulmonary arterial BP with subsequent reduction in cardiac output.¹⁵ In spite of few number of cases in our report, this may point to the possible effects of sofosbuvir on the autonomic nervous system and/cardiocardiovascular regulatory mechanisms; an observation that needs further evaluation and post marketing follow up as well as good pretreatment cardiovascular assessment because patients with syncope have an increased risk of life threatening trauma up to death.

Conclusion

Syncope may be a side effect to sofosbuvir therapy which may result in serious problems to the patient such as accidents, falls and head or limb injuries. The probable mechanism may be autonomic nervous system dysfunction leading to reflex or initial orthostatic hypotension.

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Conflict of interest

Author declares that there is no conflict of interest.

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