Novel Diuretic Effect of SGLT-2 Inhibitors: A Possible Option to Relieve CCB-induced Pedal Edema?

Prakash Hazra¹, Jignesh Ved², Mansij Biswas³
¹Interventional Cardiologist, Head of Department of Cardiology, AMRI Hospitals, Dhakuria, Kolkata, West Bengal, ²Team Lead Medicine, ³Senior Medical Advisor, Boehringer Ingelheim India, Mumbai, Maharashtra

Sir,

We read, with keen interest, the analysis by Hallow KM and colleagues on the uniqueness of SGLT2-i mediated diuretic action.¹ Through greater free-water clearance, these agents could exert a more specific effect on the interstitial fluid volume rather than the blood volume, thus possibly contributing to certain warranted clinical effects, and lesser hemodynamic compromise. In this regard, we could hypothesize the effect of SGLT2-i agents, on the pedal edema induced by calcium channel blockers (CCBs). Pedal edema is a well-recognized adverse reaction of the CCBs.² Due to the preferential dilatation of arterioles in comparison to venules, the resultant increase in capillary hydrostatic pressure causes extravasation of the fluid into the interstitial compartment. Absolute incidence of this side effect is not exactly determined because of widely varying reported rates, which may arise from differences in the surveillance technique. Active surveillance studies documented one fourth of patients who received amlodipine 10 mg per day may experience oedema.³ Use of a diuretic agent may not help in managing the pedal edema, as the diuretic agents have a predominant effect on reducing blood volume, as compared to the interstitial fluid volume. However, a private insurance database-based study from the US found an excessive use of loop diuretics following initiation of high dose CCBs, not explained by regular clinical practice or hypertension progression, thus raising concerns of unnecessary prescribing cascade.⁴ The SGLT2-i agents, on the other hand, may help in addressing a CCB-induced pedal edema, through a predominant effect on the interstitial fluid volume.⁵ In this context, we report here a case of amlodipine induced...
pedal edema, which was considerably resolved following the administration of empagliflozin.

A 62-year old male patient had a prior history of hypertension, type-2 diabetes, and coronary artery bypass grafting. He was managed with metformin (1gm twice daily), glimepiride (4mg once daily), amlodipine (10mg once daily), hydrochlorothiazide (12.5mg once daily), telmisartan (80mg once daily) and rosvastatin (20mg once daily). He had developed amlodipine-associated pedal-edema. One year later, the patient presented with severe hypotension and hypokalemia, for which he was hospitalized and managed with hypertonic saline, as well as potassium replacement. At discharge, he was reinstated on amlodipine, telmisartan, rosvastatin and metformin, at pre-event dosing regimen. Hydrochlorothiazide and glimepiride were discontinued, and replaced with metoprolol (50mg once daily) and empagliflozin (25mg once daily). The patient had persistent complaints of bilateral pedal edema in the morning, with tightening of shoes. Over the subsequent 2 months of therapy, the edema had decreased to a considerable extent; however, mild edema did persist. The patient also reported weight loss and good control of blood glucose and blood pressure.

In a patient ineligible for diuretic therapy or when use of it is inappropriate, and he is suffering from amlodipine-induced pedal edema despite receiving a high dose of angiotensin-receptor blocker, addition of empagliflozin resulted in a considerable resolution of pedal edema, apart from its known effects on cardio-metabolic outcomes. Although merely a case report, this may serve as a clinical proof of principle, for the unique diuretic mechanism of the SGLT2-i agents as described by Hallow et al.1 This observation, with further exploration on these lines, can have promising clinical implications for patients with comorbid hypertension as well as type-2 diabetes, who are appropriate candidates for receiving a CCB and an SGLT2-i agent.

Disclosure

Jignesh Ved and Mansij Biswas are employees of Boehringer Ingelheim (India) Pvt. Ltd. Their contribution to this manuscript represents their independent academic perspectives related to the topic and does not suggest in any way, the opinion of Boehringer Ingelheim.

References