CASE REPORT

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Teneligliptin-induced Allergic Rhinopharyngitis

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Introduction

Teneligliptin – a novel DPP IV inhibitor is evolving as a drug of choice for managing both drug naïve and as an add-on therapy for previously diagnosed diabetics on other oral hypoglycaemic agents, this is in part due to low cost of therapy and a favourable adverse effects profile of the drug. Teneligliptin has dual (both renal and hepatic) mode of excretion, long biologic half-life (26.9 hours) and requires no dose modification in hepatic and renally compromised patients. There have been anecdotal incidences of increased allergic events pertaining to the respiratory tract and skin with the usage of various DPP IV inhibitors. This case report highlights one such case that we encountered where teneligliptin exposure in a known diabetic, on glimepiride therapy precipitated allergic symptoms of upper respiratory tract.

Case history

A 45-year-old diabetic female came to the OPD for the management of uncontrolled hyperglycaemia. She was on glimepiride 2 mg and metformin 500 mg daily. Her blood sugar fasting was 136 mg/dl and post-prandial was 210 mg/dl, her HbA1c was 7.8. She was further advised to take teneligliptin 20 mg 1 OD for glycaemic control but the next day she came with complaints of running nose/ breathlessness/nasal stuffiness/cough/severe burning sensation in throat 2 hours after ingestion of teneligliptin tablet. She was advised to stop the drug immediately and for symptomatic treatment she was advised oral antihistaminic, cough suppressant, and saline nasal drops on which her symptoms decreased in the next 24 hours. After 15 days she was again prescribed tablet teneligliptin by some other physician for hyperglycaemia, followed by recurrence of similar symptoms. She visited our OPD and she was asked to stop teneligliptin and was advised the same symptomatic treatment as advised before. Her symptoms again responded well to it. This case brought into our notice this rare side-effect of teneligliptin.

Discussion

Teneligliptin is a third generation DPP-4 inhibitor approved for treatment of type 2 diabetes. It is currently available in Japan, South Korea, Argentina, and India. It is under pre-registration in Indonesia and under phase I trials in the US and phase II trials in Denmark, Germany, Hungary, Lithuania, Poland, Romania, and the UK[1]. Teneligliptin offers a pharmacodynamic advantage with unique "J-shaped anchor-lock domain" which signifies for its potent and long duration of action. It also offers a pharmacokinetic advantage with a long half-life of 26.9 hours and a convenient once-daily administration as an oral unit dosage form. It has a dual mode of elimination via renal and hepatic routes which sheds the burden of its clearance and can be a preferred choice for the treatment of patients with renal and mild-to-moderate hepatic impairment[2]. DPP IV inhibitors like sitagliptin and vildagliptin have been associated with stuffy and runny nose and sore throat – nasopharyngitis[3]. Aetiogenesis of such symptoms has been attributed to accumulation of substances such as substance P, eotaxin, and neuropeptide Y, etc., in the upper respiratory tract mucosa[4]. The effects of substance P are blunted by angiotensin converting enzyme (ACE), neutral endopeptidase, and DDP-4. Notably, angioedema in patients on ACE inhibitors is accompanied by low concentration of circulating DPP-4[5]. During ACE inhibition, DPP-IV inactivates substance P. Studies in rodent models suggest that substance P contributes to the pathogenesis of ACE inhibitor-associated angioedema. Thus certain studies suggest that genetic deficiency or pharmacological inhibition of DPP-IV predisposes to ACE inhibitor-associated angioedema by decreasing the degradation of substance P. In fact it has been reported that overall there was no association between vildagliptin use and angioedema in the pooled analysis; however, concomitant use of vildagliptin and ACE inhibitor was associated with a 9-fold increased risk of angioedema[6].

The symptoms in our case appeared after introduction of teneligliptin in an otherwise asymptomatic patient and waned off promptly after discontinuation of the same on to reappear after reintroduction. The patient's symptoms also responded to antihistaminic suggesting mucosal hyper-reactivity of allergic origin. Although literature is replete with case reports of other DPP IV inhibitors causing allergic adverse effects involving upper respiratory tract and skin

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but teneligliptin per se has not been incriminated with such symptoms, a literature search in PUBMED with keywords 'teneligliptin', 'respiratory allergy', led to 'zero' search results. This case reports also highlights the dose limiting nature of such adverse effects.

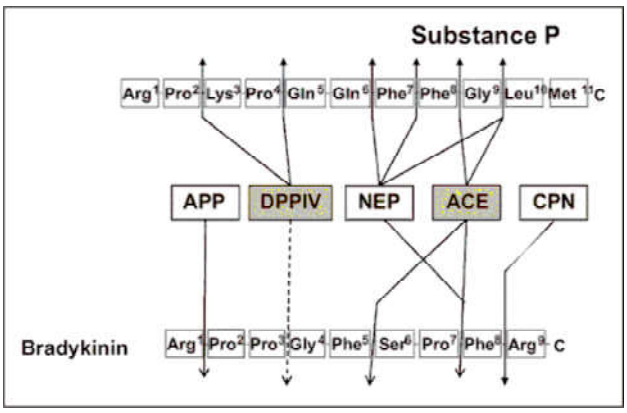

Fig. 1: *Schematic diagram showing the role of angiotension-converting enzyme (ACE) and dipeptidyl peptidase-IV (DPP-IV) in the degradation of bradykinin and substance P. Studies in rodents suggest that DPP-IV is the primary enzyme responsible for the inactivation of substance P when ACE is inhibited. The dotted line indicates that bradykinin is already inactivated by aminopeptidase P (APP) before it is degraded further by DPP-IV. CPN indicate carboxypeptidase N; NEP, neutral endopeptidase.*

On applying the Naranjo ADR scale in our case, a score of 6 was obtained which falls under the probable ADR category. Apart from allergic rhinopharyngitis, other serious adverse drug reactions such as urticaria, laryngeal oedema, angioedema, or asthma[7] have not been associated with DPP IV inhibitors. However, when used concomitantly with ACE inhibitors then the incidence of ACE inhibitor-associated angioedema was increased 9-folds[6]. It has been found that DPP IV inhibitors can be safely used in patients with asthma and it does not affect the control of asthma[7] and as such there is no report which would suggest that DPP4 inhibitors worsens any pre-existing allergies. Thus, it may be safely prescribed to patients with pre-existing asthma or allergies. As far as allergic rhinopharyngitis is concerned, an appropriate management would be withdrawal of the incriminating drug and concomitant use of an antihistaminic.

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