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Sitagliptin Intolerance

To the Editor

In type 2 diabetes mellitus, the actions and secretion of insulin are impaired, as opposed to the absolute deficiency of insulin which occurs with type 1 diabetes mellitus. Type 2 diabetes has traditionally been treated in a stepwise manner.[1] The treatment has started with lifestyle modifications, exercise, and later on, pharmacotherapy with oral and parenteral agents.[3] Sitagliptin is one of the dipeptidyl peptidase-4 (DPP-4) inhibitors which represent a new therapeutic approach.[4] Side effects of sitagliptin include upper airway symptoms mimicking rhinitis. Allergic rhinitis is frequent in the Turkish population (16%).[2] Rhinitis is one of the most frequent and disabling illnesses affecting the general population. The history of symptoms, medication and disease is important to be able to distinguish between allergic or non-allergic rhinitis, and also for diagnosis and treatment.

Fifteen type 2 diabetics were selected from the whole diabetic population admitted and were followed up for blood glucose regulation in 2008–2009 in Fatih University Hospital. Those patients who had unregulated blood glucose with other antidiabetic drugs received sitagliptin for accepted indications. Two diabetics among them developed nasal congestion, postnasal drip, wheezing, and fatigue. There was no accompanying medication associated with nasal and pulmonary symptoms such as ACE inhibitors and/or beta blockers. The Ear-nose-throat and department of pulmonary and allergic diseases consultations revealed no noticeable findings. The symptoms were resolved completely within three days after drug withdrawal for these two patients. The others who received sitagliptin did not have any complaint about medication.

In the first case a 66 year-old woman who was diagnosed with type 2 diabetes mellitus 10 years ago was admitted to the endocrinology clinic with the complaint of postnasal drip, cough and fatigue at the 10th day of sitagliptin use. She had a history of hypertension. She was prescribed sitagliptin for diabetes and followed up for blood glucose regulation. Ten days after initialising the sitagliptin treatment she had symptoms of rhinitis, nasal congestion, postnasal drip, wheezing, and fatigue. She was evaluated for atopic aetiology with skin prick tests. Skin prick tests were negative for mites, moulds, pollens, animal dander and feathers. The symptoms were resolved after the fourth day of drug withdrawal.

In the second case a 52 year-old woman who was followed up with type 2 diabetes mellitus for 25 years presented with the complaints of nasal congestion, postnasal drip, throat pain, cough and fatigue after 15 days using sitagliptin. She had also history of hypertension requiring no medication. She was prescribed sitagliptin for glycaemic control. She did not have any history of atopy. Skin prick tests were also performed for this patient and were negative. The symptoms were resolved after the third day of drug withdrawal. Due to the severity of the symptoms, we were unable to re-introduce the drug to determine whether the symptoms would return.

Type 2 diabetes mellitus is characterised by two major pathophysiological defects: (1) insulin resistance, which results in increased hepatic glucose production and decreased peripheral glucose consumption, and (2) impaired β-cell secretory function.[1]

Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new therapeutic approach for the treatment of type 2 diabetes.[4] These agents work by inhibiting the DPP-4 enzyme that degrades incretin hormones such as glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP). Active GLP-1 and GIP stimulate glucose-dependent insulin biosynthesis and release, and GLP-1 also suppresses glucagon release, delays gastric emptying, and increases satiety.[5] In patients with type 2 diabetes, chronic treatment with DPP-4 inhibitors decreased postprandial glucose excursion, fasting plasma glucose, and haemoglobin A1c (HbA1c), and was well tolerated with neutral weight effects and a low incidence of hypoglycaemia and gastrointestinal adverse events relative to placebo.[6]

One of the DPP-4 inhibitors is sitagliptin, which is a potent, competitive, reversible inhibitor of the DPP4 enzyme, and is the first agent in this class to be used.[7]

Medication with DPP-4 inhibitors appears to be reasonably safe.[8] There was also slightly higher incidence of constipation, nasopharyngitis, pharyngitis, pharyngolaryngeal pain, rhinitis, urinary tract infection, myalgia, arthralgia, hypertension, and dizziness.[9] In our cases, these side effects did not occur. Rhinitis and other upper airway symptoms were seen in our two cases although it has been reported that

there is no significant difference in the incidence of these side effects in sitagliptin-treated patients compared with normal population.[10] In our cases the incidence of rhinitis and upper airway symptoms was significantly high.

Most trials of sitagliptin in combination with other oral antidiabetics showed that DPP-4 inhibitors provide incremental and additive improvements in glycaemic parameters.[11]

Recently, post-marketing reports of anaphylaxis, angio-oedema and rashes, including Stevens-Johnson syndrome, in sitagliptin-treated patients have emerged. However, no established casual relationship has been established. Kidney malfunction was a contraindication.[8]

We report two cases of non-allergic rhinitis due to medication of sitagliptin. Rhinitis is one of the most frequent and disabling illnesses affecting the general population. It generally has an allergic background. The history of symptoms, medication and disease is important to be able to distinguish between allergic or non-allergic rhinitis, and also for diagnosis and treatment.

We propose that the symptoms of rhinitis might occur because decreased DPPIV activity induced by enzyme inhibition enhances the production of airway mucosal peptides. These might activate mucus secretion (generation of secretogogues), sensory nerves (cough afferents), large airway obstruction (bronchoconstrictors), and central nervous system mediated fatigue. There was no study which showed the relationship between DPP-4 inhibitors and inflammation of upper airway mucosa. DPP-4 inhibitors and its effects must be investigated with further studies -it must be shown in vivo whether there is an association between DPP-4 inhibitors and inflammation of upper airway mucosa.

In conclusion, however, sitagliptin appears to be reasonably safe, side effects including upper airway symptoms might be a reason for drug withdrawal and history of sitagliptin medication should be considered as a reason for non-allergic rhinitis. More studies are needed to investigate DPP-4 inhibitors and its effects on upper airway mucosa.

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