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Need for Monitoring of Adverse Drug Reactions in Diabetic Patients Induced by Sitagliptin-A Mini Review

Kalaiselvan V, Pramod Kumar A*, Agrawal V and Singh A

Department of Health & Family Welfare, National Coordination Centre-Pharmacovigilance Programme of India, India

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***Corresponding author:** Pramod Kumar A, Indian Pharmacopoeia Commission, National Coordination Centre-Pharmacovigilance Programme of India, Ministry of Health & Family Welfare, Govt of India, Raj Nagar, Ghaziabad, Uttar Pradesh, India, Email: pramod_pharmacist@yahoo.com

Introduction

Diabetes is rapidly gaining the status of a impending epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. According to Wild et al. the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030. India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country [1-3].

The International Diabetes Federation (IDF) estimates the number of people with diabetes in India will reach 80 million by the year 2025. There are at least seven different classes of agents used as immunotherapy, or in combinations for the treatment of diabetes mellitus. These include biguanides, sulphonylureas, meglinitides, alpha-glucosidase inhibitors, thiazolidinediones (TZD), glucagon like peptide-1 (GLP-1) agonists and insulin [4,5]. Gliptin are orally administered dipeptidyl peptidase 4 (DPP-4) inhibitors which prolongs the action of in cretin hormones, including glucagon-like peptide 1 and glucose-dependent insulin tropic polypeptide, by inhibiting their breakdown. It improves glycemic control in patients with type 2 diabetes (T2DM), primarily by suppressing glucagon levels and increasing endogenous insulin secretion. Sitagliptin is helpful in lowering HbA1c, and fasting as well as postprandial glucose in immunotherapy and in combination with other oral anti diabetic agents [4].

The first drug off the blocks was Sitagliptin, the first DPP-4 inhibitor which was approved in 2006 and is now available for use globally including India, Sitagliptin is approved by the FDA as an adjunct to diet and exercise to improve glycaemic control in patients with T2DM, either as a immunotherapy, or in combination with metformin or thiazolidinediones [5]. Compared to other oral hypoglycemic agents, gliptins produce similar reductions in blood glucose glycated hemoglobin (HbA1c) levels, but they offer several attractive clinical advantages. A slight risk of hypoglycemia, especially much lower than that observed with sulfonylureas, weight neutrality, contrasting favorably with the weight gain generally observed with sulfonylureas and thiazolidinediones (TZDs) are the key points, which make the gliptins stand out. Therefore, it is no surprise that this pharmacological class is expected to play an greater role in the management of T2DM. The gliptins as a class also exhibit considerable heterogeneity amongst themselves in terms of substrate selectivity and pharmacokinetics of the different members of this family. Sitagliptin is the most selective DPP-4 inhibitor available at present [6].

DPP-4 inhibitors have become a research area of intense focus with a number of pharmaceutical companies involved in the development of a new diabetes therapy. As of this writing, there are more than 20 different DPP-4 inhibitors being developed for various therapeutic interests-mainly T2DM. Although, a number of DPP-4 inhibitors have been described, all have limitations relating to potency, stability or toxicity. Sitagliptin and vildagliptin are two DPP-4 inhibitors that have been approved in India for human use in October 2007 and January 2008, respectively [7].

A study reveals DPP-4 inhibitors significantly reduced HbA1c at 24 weeks by 0.6% (0.5–0.7%) when compared with placebo; they showed a similar efficacy in immunotherapy and in combination [8]. They appear to be more effective in older patients with mild/ moderate fasting hyperglycemia [9]. A 24-week no inferiority trial comparing the efficacy of Sitagliptin and metformin as immunotherapy in T2DM patients (whose mean baseline HbA1c was 7.2), the mean changes in HbA1c

were -0.43 and -0.57%, respectively. Sitagliptin is well absorbed (approximately 80% excreted unchanged in the urine) with an apparent terminal half-life ranging from 8 to 14 hours. Renal clearance of Sitagliptin averaged 388 mL/min and was largely uninfluenced by the dose administered. Sitagliptin was well tolerated and is not associated with hypoglycemia [10].

As Sitagliptin is commonly reported to cause headache, irritability, drowsiness, hunger, weakness, tachycardia, dizziness, sweating, sore throat, back pain, nausea, stomach pain, diarrhea, constipation and confusion [11]. The Pharmacovigilance Programme of India data base was analysed and found that the most common System Organ Class which was affected due to the use of Sitagliptin is 'metabolic and nutritional disorders' and the commonest ADR was found to be 'Glucose tolerance impaired' with 41 reported ADRs. This is followed by 'Gastrointestinal disorders' with commonest ADR Diarrhea with 16 ADRs.

Indian Pharmacopoeia Commission (IPC) is functioning as National Coordination Centre (NCC) for Pharmacovigilance Programme of India (PvPI) to track all the adverse drug reactions (ADR) in Indian population [12]. Health care professionals are urged to report ADRs due to Sitagliptin because sometimes it contributes to the emergence of new disorders/reactions. To report all such events, NCC-PvPI has extended its reach throughout the country by launching Helpline 1800 180 3024 (toll free) to report ADRs. Healthcare professionals (HCPs)/ Consumers can report ADRs associated with treatment therapies, whether known or unknown, serious or non-serious, and frequent or rare by filling the Suspected ADRs Reporting Form and can submit to nearby PvPI (available at www.ipc.gov.in) [13].

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