Research Article

Anti-Diabetic Prescriptions Evaluation for Metformin, Sitagliptin and Gemigliptin among Early Moderate Grade New Type II Diabetes Mellitus Patients in Global Tertiary Care Hospitals: An Analytical Study in Rational Pharmacotherapeutics

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ABSTRACT

Introduction: Diabetes mellitus type II is globally very common, yet neglected. Inhibition of dipeptidyl peptidase–4 by DPP–4 inhibitors enhances hormonal activity of incretins (GLP–1, GIP, GRP), stimulates insulin release and reduces glucagon secretion, thus producing anti-hyperglycaemic activity in type II diabetes mellitus patients.

Objective: Anti-diabetic prescriptions evaluation for metformin, sitagliptin and gemigliptin among early moderate grade new type II diabetes mellitus patients in global tertiary care hospitals: An analytical study in rational pharmacotherapeutics.

Materials and methods: 100 new early moderate grade type II diabetes mellitus patients, were prescribed oral metformin 500 mg once daily, sitagliptin 25 mg once daily or gemigliptin 25 mg once daily for 3 months, in monotherapy, or in combination therapy, or in a mixed regimen of monotherapy and combination therapy. The completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug in the prescriptions, were evaluated and analysed.

Results: 100% of the prescriptions contained completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug.

Key Words: Biguanides; Metformin; Dipeptidyl peptidase-4 inhibitors; Sitagliptin; Gemigliptin; Prescriptions evaluation

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INTRODUCTION

The American Association of Clinical Endocrinologists (AACE) provides guidelines for type II diabetes mellitus management, which include lifestyle therapy, medically assisted weight loss, and individual goals of achieving haemoglobin A1c (HbA1c) level of ≤ 6.5%. The patient characteristics, like glycaemic index and weight, lifestyle, co-morbidities and undesirable side effects of pharmaco-therapeutic management, determine the choice of antidiabetic agents. The commonly associated side effects with oral anti-diabetic agents are hypoglycaemia, weight gain due to hyperinsulinemia, gastrointestinal symptoms, and hepato-renal toxicity. The increase in adverse effects demands a safer antidiabetic agent. The critical effects under consideration are the drug's potential for hypoglycaemia, weight gain, and long term side effects [1].

Metformin, has improved outcomes, as a mono-therapeutic as well as a combination anti-diabetic drug, overcoming insulin resistance and lowering serum glucose levels, by the activation of 5'Adenosine Mono Phosphate (AMP) activated protein kinase. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. It has beneficial effects on HbA1C and weight [2]

Inhibition of dipeptidyl peptidase–4 by dipeptidyl peptidase–4 inhibitors enhances the hormone activity of incretins, like glucagon like peptide–1 and other bioactive peptides (glucose-dependent insulino-tropic polypeptide, gastrin releasing peptide), thus stimulating the release of insulin and reducing the secretion of glucagon's, when given in monotherapy or in combination with metformin. This effect decreases the blood glucose levels as well as HbA1c levels in type II diabetes mellitus patients, without causing severe hypoglycaemia [3,4].

MATERIALS AND METHODS

Inclusion Criteria

The inclusion criteria are as follows:

(i) Patients of any gender,

(ii) Patients within 35 and 60 years,

(iii) Patients presenting with new type II diabetes mellitus, of early moderate grade,

(iv) Type II Diabetes mellitus American Diabetes Association diagnosis criteria,

(v) co-operative and conscious patients,

(vi) Patients willing to undergo all pre and post-treatment investigations and willing to complete the entire course of treatment,

(vii) Patients who have given consent and are willing to go for a follow-up,

(viii) Patients not taking any previous anti-diabetic drug,

(ix) Patients not taking any concomitant medication.

Exclusion Criteria

The exclusion criteria are as follows:

(i) Uncooperative or unconscious patients,

(ii) Patients below 35 and above 60 years,

(iii) Patients presenting with any grade other than early moderate grade of diabetes,

(iv) Patients with a history of hypersensitivity to any of the study drugs,

(v) Patients with high risk diseases or co-morbidities,

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(vi) Cardiac, renal or any other associated complications or co-morbidities,

(vii) Any chronic disease intervening with the study data,

(viii) Pregnant or lactating women,

(ix) Paediatric or geriatric patients,

(x) Other associated medical illness or disorders, having impact on study results,

(xi) Female patients using hormonal contraceptives.

Study Design

A global, multi-centre, retrospective, observational and analytical study of the clinical prescriptions was performed.

Study Population

The study population consisted of 100 treated new type II diabetes mellitus patients, of early moderate grade.

Study Period

The study period, comprising of the periods for the research study and the compilation of the study literature, was 4 months, from October, 2020 to February, 2021.

Place of Study

The research study and the compilation of the study literature was done in the Departments of Pharmacology, Clinical Pharmacology, Pharmacovigilance, Internal Medicine, Endocrinology, Pathology and Clinical Pathology, in Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Hazra Nursing Home, Rama Medical College Hospital and Research Centre, J.J.M. Medical College and Hospital, K. D. Medical College Hospital and Research Centre and Hi-Tech Medical College and Hospital.

Study Procedure

100 new early moderate grade type II diabetes mellitus patients, were prescribed oral metformin 500 mg once daily, sitagliptin 25 mg once daily or gemigliptin 25 mg once daily for 3 months, in monotherapy, or in combination therapy, or in a mixed regimen of monotherapy and combination therapy.

The patients' characteristics, diabetic symptoms assessment, patients' disease and disease-related history were recorded with a proforma. Then, thorough general physical examination and systemic examination were performed on the patients under study. The relevant blood, urine and other investigations were done to confirm the progressing health status of the patients being treated.

The efficacy assessment was done, by recording the fasting and the post-prandial blood sugar level, HbA1c level and urine routine examination findings including sugar and albumin levels and microscopy, at subsequent intervals and follow-up. The safety assessment was done by the monitoring of adverse drug reactions, at subsequent intervals, and follow-up.

- The prescription content analysis, of all the 100 prescriptions, was done. The different aspects of the prescription contents, like The completeness of the prescription contents,
- The dose of drug,
- The duration of treatment,
- The instructions of medication,
- The frequency of drug intake,
- The name of the drug and
- The dosage form of the drug was thoroughly analysed and recorded, and the various observations were statistically recorded as the prescription content analysis percentages.

Statistical Analysis

The prescription contents evaluation was performed by a statistical analysis in percentages.

RESULTS

The demographic characteristics of the patients were comparable (Table 1).

Table 1: Prescription content analysis for different Anti-Diabetic drugs.

Prescription contents	Results (%)
Completeness of prescription Contents	100 (100)
Dose of drug	100 (100)
Duration of treatment	100 (100)
Instructions of medication	100 (100)
Frequency of drug intake	100 (100)
Name of the drug	100 (100)
Dosage form of the drug	100 (100)

Table 1 depicts that the completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were found in 100% of prescriptions

The monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy of Metformin, Sitagliptin or Gemigliptin, was observed to be quite efficacious, which had controlled type II diabetes mellitus among new patients, with significant decrease in the blood sugar levels and the HbA1c levels, in the successive 3 months. The adverse effects observed with monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, was statistically non-significant. Therefore, the monotherapy, or combination therapy, or mixed regimen of monotherapy and combination therapy, were safe and tolerable.

DISCUSSION

Diabetes, which is a chronic metabolic disorder, has recently sharply increased on a global scale. According to the International Diabetes Federation (IDF), there were 415 million patients diagnosed with T2D. Diabetes among Asian populations has some distinguishing characteristics from other races in the world, namely the early decrease in beta-cell function resulting in high postprandial blood glucose and the development to chronic diabetic complications occurs at an early stage of the disease. Hence, a therapeutic agent who increases beta-cell function plays an important role in anti-hyperglycemic protocols [5].

Nowadays, anti-DPP4 anti-hyperglycemic agents have been widely used for patients with T2D under guidelines of diabetes associations and proved to be effective in the enhancement of beta-cell function

via ameliorating serum incretin hormone concentrations (two major incretins, GLP-1 and glucose-dependent insulino tropic polypeptide, GIP) an anti-beta-cell apoptosis agent. There have been two incretin-related therapies for patients with T2D, namely glucagon-like peptide-1 agonists, exedin-4 and dipeptidyl peptidase-IV inhibitor, sitagliptin. In 2009, the American Association of Clinical Endocrinologists (AACE/ACE) issued the guideline for anti-hyperglycemic treatment protocol which mentioned about the usage of incretin therapies as the first-line drug for newly diagnosed patients with T2D (i.e., incretin therapies could be monotherapy or in combination with other antidiabetic drugs such as Biguanides, Sulfonylureas, or Insulin). These days, incretin therapies regarding treatment for patients with T2D have been developed on a global scale and shown positive effects on not only glycaemic control but prevention from chronic diabetic complications as well. Whilst anti-DPP4 agents have many effects on anti-hyperglycaemic conditions, there have been little researches on the Asian population to investigate the role of these drugs on beta-cell function, peripheral insulin sensitivity, insulin resistance and serum GLP-1 concentrations in comparison to healthy subjects but results were controversial [6].

GLP-1 is potent insulin secretion that exhibits glucose dependent insulin secretion. In vitro study, GLP-1 was found to be capable of healing beta-cell function which was reduced with age for some reasons:

i. Recruit beta-cells into a secretory mode

ii. Activate the gene for glucose sensitivity of beta-cells and

iii. Reduction of beta-cell apoptosis.

Treatment of old Wistar rats with GLP-1 led to the normal insulin secretion via increases of beta-cell mass and pancreas cell proliferation. And, it was hypothesized that besides the hypoglycaemic effect of anti-DPP4 agents, it may be the increase of GLP-1 that contributed to the increase of beta-cell functions. In another study, serum GLP-1 concentrations increased sharply after treatment and regression analysis confirmed that serum GLP-1 concentrations were independent variable making a great contribution to the amelioration of insulin sensitivity and insulin resistance. It was found that there were improvements in beta cell function but there were also 4 patients who still had low beta cell functions in comparison to those in the control group [3].

Recent studies have suggested that SARS-CoV-2 may also bind dipeptidyl peptidase 4 (DPP-4 or CD26) when entering cells of the respiratory tract. Based on the modelling of SARS-CoV-2 structure and receptors, it has been also postulated that DPP-4 may facilitate the SARS-CoV-2 entry into target cells, due to its high homology with Middle East respiratory syndrome coronavirus. The interplay between the SARS-CoV-2 spike glycoprotein S1 and human DPP-4 may represent a potential factor that promotes SARS-CoV-2 hijacking and virulence, and inhibition of this interaction may thus have the potential to improve clinical outcomes of COVID-19. Sitagliptin is an oral and highly selective DPP-4 inhibitor with glucose-lowering effects and it was approved by the Food and Drug Administration in 2006 as an Anti-Diabetic drug due to its efficacy in increasing the bioavailability of glucagon-like peptide 1 (GLP-1). This molecule is also known for its immune regulatory and anti-inflammatory effects. Sitagliptin has been shown to have the potential to inhibit Hepatitis C virus replication, to suppress Chemokine release, and to reduce Interleukin-6 production. Interestingly, Sitagliptin showed high selectivity for DPP-4 and may have favourable effects on B-cells by exerting an anti-inflammatory function. Based on all of the aforementioned premises, DPP-4 inhibition has been suggested to be of potential benefit for patients with COVID-19, particularly in those with type 2 diabetes. Interestingly, while type 2 diabetes does not increase susceptibility to SARS-CoV-2 infection, type 2 diabetes has been associated with worse outcomes of COVID-19. [4].

CONCLUSION

In this study, the completeness of the prescription contents, the dose of drug, the duration of treatment, the instructions of medication, the frequency of drug intake, the name of the drug and the dosage form of the drug were found in 100% of prescriptions. Type 2 diabetes increases the mortality risk in patients with COVID-19, particularly in those with more severe disease. In patients with type 2 diabetes and COVID-19, poorly controlled blood glucose levels are associated with markedly higher mortality as compared with subjects with better metabolic control. The prescription content analyses showed 100% completeness.

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Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6), and in compliance with the regulatory requirements. An informed consent was obtained from each patient.

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