INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

A STUDY OF THE POSSIBLE DRUG-DRUG INTERACTIONS INVOLVING ORAL ANTIDIABETIC DRUGS IN PATIENTS WITH TYPE II DIABETES

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Article Received on: 26/02/19 Approved for publication: 08/04/19

DOI: 10.7897/2230-8407.1005180

ABSTRACT

Background of Study: Incidence of diabetes is increasing due to increase in the prevalence of risk factors of this disease. Diabetes is also a risk factor for other diseases especially cardiovascular diseases. Increase in co-morbidities results in polypharmacy which in turn increases possibility of drug interactions. This study was conducted to evaluate the prevalence of possible drug interactions involving oral hypoglycaemic agents in Type II diabetes mellitus patients. Methods and Findings: This is a prospective, observational study, conducted for a period of 6 months, from September 2017 to February 2018. Type II diabetes mellitus patients with prescription of one or more oral hypoglycaemic drugs were included in the study. The demographics, and drug therapy related details of patients were recorded in the specially designed patient profile form. The drug interactions were assessed using Micromedex 2.0, Medscape and www.drugs.com. Results: A total of 136 interactions were reported in 63 patients. We detected 63 possible moderate interactions. Between oral hypoglycaemic agents. Interaction between Metformin and Salbutamol was most commonly seen interaction. Metformin and Glimepiride were the oral hypoglycaemic agents most commonly involved in drug interactions. Conclusion: Glimepiride and metformin were most commonly involved oral hypoglycaemic agents involved in drug interactions. Impairment of blood glucose control, increase in the risk of lactic acidosis, increase in the prevalence of hypoglycaemia, masking the effects of hypoglycaemia were the most common expected complications of these interactions. Therefore constant monitoring of the above symptoms is required while prescribing the mentioned combinations.

Keywords: Type II diabetes mellitus, oral hypoglycaemics, interaction, metformin

INTRODUCTION

In diabetes pancreas does not produce required insulin or body does not use the insulin it produces. It is a serious, chronic disease which has turned into an important public health problem, one of four priority non-communicable diseases (NCDs) targeted for action by world leaders. Increase in the risk factors of diabetes in the recent times has resulted in increase in number of cases and increase in the prevalence of diabetes.[1] The latest figures from the International Diabetes Federation (IDF) indicate that as of 2015 more than 415 million people worldwide have diabetes. This number is expected to increase to 642 million by 2040.[2]

Diabetes is accompanied by other co morbidities like hypertension, hyperlipidaemia, depression, which requires additional pharmacotherapeutic agents. Polypharmacy can give rise to non-compliance, increase in adverse drug reactions and drug interactions. It is observed that the drug-drug interactions make up to 30 % of all the adverse drug events. Drug interactions can interfere negatively and to the patient's health outcomes and can be an economic burden to the entire healthcare system. Thus it is important to monitor the drug interactions in patients with diabetes.[3]

Hence the objectives of this study were to study the incidence of drug- drug interactions in type 2 diabetes mellitus patients, categorise the interactions into major and moderate. The data collected can be utilised to prevent the interactions in the future.

MATERIALS AND METHODS

This is a prospective, observational study, conducted in medicine unit of Sagar Hospitals, Bengaluru for a period of 6 months, from September 2017 to February 2018. Human ethical clearance for this study was obtained from ethical committee of Dayananda Sagar College of Pharmacy, Bengaluru (Institutional ethical clearance number – 02-02/2017). The study protocol was prepared and submitted to the Dayananda Sagar College of Pharmacy ethics committee on human subject research for ethical clearance. The study was approved by Institutional Ethics Committee and issued ethical clearance certificate for the same. All the patients of either sex admitted as inpatients, diagnosed with type II diabetes mellitus and prescribed with Oral Hypoglycaemic Agents (OHAs) alone or OHAs along with insulin were included in the study. Type II diabetes mellitus patients who were pregnant women or posted for surgery were excluded from the study.

The data required for the study was collected from patient case sheet, by conducting patient interview and from laboratory data reports. The prescriptions were chosen based on inclusion and exclusion criteria and details of the patient were followed till discharge from the patient case sheet. During the study the inpatient case record were reviewed which include patient demographics, specific information related to OHAs use such as name of the OHA, their dosage schedule, date of discontinuation, concomitant medications, lab investigations, diagnostic

procedures and treatment details. The information collected was documented in the patient profile form. The drug interactions were assessed using www.drugs.com.

RESULTS

A total of 105 patients were included in the study.

There were more number of male patients compared to female patients (Table 1). Among 106 patients of study population with age group ranging between 41 to 80 years, majority of male patients were in the age group 61 to 80 years (57.02 %) and the least were in the age group of above 81 (5.30 %) and majority of female patient of age group 51 to 60 (28 %) and the least were in the age group of above 81 (12 %) (Table 2).

Hypertension was the most commonly encountered co-morbidity with diabetes followed by chronic kidney disease, ischaemic heart disease, lower respiratory tract infection and gastroenteritis (Table 3). Maximum number of patients were prescribed with a single OHA. Only 5 % of the study population was prescribed 3 OHAs (Table 4). Sulphonyl ureas were most commonly prescribed OHA's followed by biguanides, alpha-glucosidase inhibitors, DPP4 inhibitors and sodium-glucose transport inhibitors (Table 5). A total of 63 patients suffered 136 drug interactions (Table 6).

Among the combinations with potential to cause drug interactions, metformin and salbutamol was prescribed to many patients. Severity of this interaction was moderate (Table 7)

DISCUSSION

This study was conducted to identify and analyse the possible drug interactions involving OHAs in patients with type II diabetes mellitus. The majority of the subjects included in the study were males. This observation indicates the higher prevalence of diabetes in males. This observation is similar to the study conducted by Londhe SP, *et al*.[4] But in a study conducted by Subramanian A, *et al*. female patients were more in number. In this study population majority of the patients were above 60 years of age indicating a higher prevalence of diabetes in this age group. Hypertension was the most commonly encountered co-morbidity in the study population with the incidence of 82 %.[5] Our study findings are similar to the study conducted by Pantalone KM, *et al*. where hypertension was the most common complication with diabetes with the incidence of 82 % to 87 %.[6]

Most of the patients were prescribed with a single OHA and only 5 % of study subjects were prescribed with 3 OHAs. This observation indicates that majority of the study population had controlled blood sugar levels with single OHA. A study conducted by Venkateswaramurthy N *et. al*, also reported that 79 % of patients were controlled with OHA monotherapy.[7] But in a study conducted by Yada N, *et al*. majority of the prescriptions had 2 OHAs per prescription. Biguanides were the most commonly prescribed OHAs followed by sulphonyl ureas.[8] A study conducted by Sultana M, *et al*. in university hospital in India[9] and a study by Sharma M, *et al*. in UK also reported that metformin was the most commonly prescribed OHA.[10] According to the consensus statement of 2006 from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) metformin should be initiated in the absence of contraindications, as a first line agent for newly diagnosed type II diabetes mellitus concurrent with lifestyle intervention.[11] Moreover, metformin does not induce weight gain or hypoglycaemia, and is the only diabetic treatment found to have a long-term benefit in reducing cardiovascular risks and organ damage.[10]

Most commonly encountered possible drug interaction was metformin and salbutamol. In this interaction salbutamol may interfere with the blood glucose control and reduce the efficacy of metformin in controlling the blood glucose level. Since salbutamol is administered for complaints of breathlessness, this interaction was most common. Dyspnoea was the most common presenting complaint in our study population. Hence monitoring of blood glucose levels closely is important.[12]

Next frequent possible interaction was with metformin and ranitidine which also increases the chances of lactic acidosis by increasing the metformin levels in blood.[13] Ranitidine was prescribed in most of the patients with polypharmacy to reduce heartburn.

In the third most frequent interaction, metformin and furosemide –similar to the interaction above, furosemide may increase the plasma concentrations of metformin increasing the risk of lactic acidosis and that metformin may decrease the peak concentration and elimination half-life of furosemide by 31 % and 32 %, respectively.[14]

The next frequent combination with possible interaction was aspirin and glimepiride where aspirin may potentiate the hypoglycaemic effects of glimepiride by stimulating the insulin secretion.[15]

In the next frequent possible interaction, glimepiride and salbutamol, salbutamol may increase chances of hyperglycaemia, glucose intolerance and new onset diabetes mellitus.[16]

Metformin and Clarithromycin may cause significant hypoglycemia. The mechanism behind this interaction is inhibition of the CYP450 3A4 isoenzyme by clarithromycin.[17]

In the next frequent possible interaction of metformin and spironolactone, diuretic-induced renal impairment and dehydration may increase the risk of lactic acidosis. In addition, thiazides and other diuretics are found to interfere with glucose control by causing hyperglycemia, glucose intolerance, new-onset diabetes mellitus, and/or exacerbation of pre-existing diabetes.[18]

Possible interaction of metformin and levothyroxin results in the reduced efficacy of metformin as levothyroxine can cause hyperglycemia, glucose intolerance, new-onset diabetes mellitus, and/or exacerbation of pre-existing diabetes.[19]

In the next possible frequent interaction which is between moxifloxacin and metformin, moxifloxacin interferes with the therapeutic effects metformin. Moxifloxacin interferes with the blood glucose homeostasis by influencing the pancreatic beta cell ATP-sensitive potassium channels that regulate insulin secretion.[20]

In the possible interaction of metoprolol and glimepiride, metoprolol masks some of the normal physiologic response to hypoglycaemia. Symptoms of hypoglycaemia such as tremor and tachycardia may be absent, making it more difficult for patients to recognize an oncoming episode. In addition, multiple effects on glucose metabolism have been reported.[21]

Table 1: Gender distribution of diabetic patients

Sex	No. of Patients (n = 106)	Percentage (%)
Male	56	53
Female	50	47

Table 2: The Distribution of study subjects based on age

Age Group	Total No. of Patients	No. of Males	No. of Females	% Males	% Females
41-50	18	11	7	19.70%	14%
51-60	24	10	14	17.90%	28%
61-70	27	16	11	28.60%	22%
71-80	28	16	12	28.60%	24%
Above 80	9	3	6	5.30%	12%
Total	106	56	50	100%	100%

Table 3: Co-morbid illness with diabetes mellitus

Co-morbid illness	No. of patients
Hypertension	86
Chronic Kidney Disease	22
Ischemic Heart Disease	22
Lower Respiratory Tract Infection	10
Gastroenteritis	10

Table 4: Number of OHAs per prescription

No. Of OHAS Per Prescription	No. of Patients (n = 106)
1	65 (61%)
2	36 (34%)
3	5 (5%)

Table 5: Classification of patients with interactions based on prescribed class of drugs

OHAs	Number of Patients	Percentage (%)
Sulphonyl ureas	26	15%
Biguanides	44	25%
Alpha-Glucosidase Inhibitors	14	8%
DPP4 Inhibitors	12	7%
Sodium Glucose Transport Inhibitors	4	2%
Combination Therapy	74	43%

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Table 6: Distribution of Drug Interactions

Total number of drug interactions	136
Number of patients with drug interactions	63
No. of Male patients	32
No. of Female patients	31

Table 7: Classification of Drug Interactions

Ranking	Drug Combination	No. of Encounters	Severity of interaction
1	Metformin+salbutamol	16 (22%)	Moderate
2	Metformin+ranitidine	11 (15%)	Moderate
3	Metformin+furosemide	10 (14%)	Moderate
4	Glimepiride+aspirin	7 (10%)	Moderate
5	Glimepiride+salbutamol	7 (10%)	Moderate
6	Metformin+clarithromycin	6 (8%)	Moderate
7	Metformin+spironolactone	5 (7%)	Moderate
8	Metformin+levothyroxine	4 (5%)	Moderate
9	Metformin+moxifloxacin	4 (5%)	Moderate
10	Glimepiride+metoprolol	3 (4%)	Moderate

In general both possible pharmacokinetic and pharmacodynamics interactions involving OHAs were reported in this study. Though the effects were not reported by patients, close monitoring by pharmacist may result in better and optimal management patient's symptoms. The class of drugs involved in interaction include bronchodilators, antihypertensives, antibiotics, antacids and antiplatelet drugs. This observation can be correlated with the co-morbid conditions of type II diabetes mellitus patients.

CONCLUSION

In this study which was conducted in patients with type II diabetes mellitus on OHAs. All reported possible interactions were

moderate in nature. Glimepiride and metformin were most commonly involved OHAs. Impairment of blood glucose control, increase in the risk of lactic acidosis, increase in the prevalence of hypoglycaemia, masking the effects of hypoglycaemia were the most common complications of possible interactions involving OHAs. Therefore, constant monitoring of the above symptoms is required while prescribing the mentioned combinations.

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Cite this article as:

Sapna K Dongre *et al*. A study of the possible drug-drug interactions involving oral antidiabetic drugs in patients with type II diabetes. Int. Res. J. Pharm. 2019; 10(5):141-144 http://dx.doi.org/10.7897/2230-8407.1005180

Source of support: Nil, Conflict of interest: None Declared