RESEARCH ARTICLE

Utilization of Some Newer Oral Antidiabetic Agents in a Tertiary Care Hospital

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Received: 15.02.2012
Accepted: 13.06.2012

DOI:10.5455/njppp.2012.2.146-151

ABSTRACT

Background: Type 2 diabetes mellitus (DM), a common metabolic disorder, prevalence of which is predicted to rise in virtually every country with the greatest increase expected in developing countries. Modification in diet and life style are usually insufficient to provide good, long-term metabolic control of type 2 DM; pharmacological adjuvants are required in majority of patients. As there is no recommended regimen, it is difficult to choose an antidiabetic agent from the available groups which become even more complex by rapidly introducing newer agents.

Aims & Objective: To evaluate prescribing pattern of newer oral antidiabetic agents in a tertiary care hospital.

Materials and Methods: Prospective observational study was conducted for one year in the diabetic out patient department (OPD) at Civil Hospital, Ahmedabad. A total 290 randomly selected patients of all age groups and either sex of type 2 diabetes mellitus were observed and details were recorded in a predesigned case record form. FBS level of 120mg% and PPBS level of 150 mg% was considered for achieving satisfactory blood sugar control.

Results: Among the patients who had undergone blood sugar analysis at the time of study, FBS level was 120 mg% in 48 (22.42%) patients while PPBS level was 150mg% in 21 patients (9.81%) only. Oral antidiabetic drugs alone were prescribed in 242 (83.45%) patients while insulin was added along with oral antidiabetic agents in rest of patients. Among patients receiving oral antidiabetic drugs, monotherapy was prescribed in only 43 (14.83%) patients while in the rest of the patients combination therapy was prescribed. Among oral antidiabetic combination, glipizide along with metformin is the most commonly prescribed combination in 112 (38.42%) patients. Among newer agents, pioglitazone was the most commonly prescribed agent but only in combination with other oral antidiabetic agents. Pioglitazone was prescribed with glipizide and metformin in 44 (15.17%) patients while along with metformin and glimepiride in 10 (3.45%) patients. Patients who had diabetes for five years or less could be managed with single oral agent while two or three agents were required in patients having diabetes for more than this period.

Conclusion: Adequate management of diabetes mellitus is difficult to be achieved with a single oral agent. Most of the patients require two or more drugs to achieve glycemic control. Newer antidiabetic agents have been prescribed in combination only. Pioglitazone has been the most frequently prescribed medication in combination with glipizide and metformin. Even with all these medications a tight glycemic control is achieved in very few patients which needs an attention.

KEY WORDS: Utilization; Antidiabetics; Pioglitazone; Sulfonylureas; Glycemic Control

INTRODUCTION

Diabetes mellitus (DM) has been known to mankind since time immemorial. Diabetes mellitus is a group of metabolic disorders resulting from absolute or relative deficiency of insulin or its function. It is estimated that the global number of persons with diabetes will rise from 151 million in year 2000 to 221 million by the year 2010, and to 300 million by the year 2025.[1] This rise is predicted to occur in virtually every country with the greatest increase expected in developing countries.[1] India has the dubious distinction of being home to the largest number of people suffering from diabetes than any other country.[2] According to a survey, 4% of adults in India suffered from diabetes in the year 2000 and it is expected to increase to 6% by 2025.[3] Modification in diet and life style are usually insufficient to produce good, long-term metabolic control of type 2 DM; pharmacological adjuvants are required in majority of patients.[4] Orally active agents are employed in the first instance and insulin is reserved for patients in whom oral hypoglycemic agents prove insufficient. While there are wide varieties of options for pharmacotherapy of diabetes, there is no one recommended regimen.[5] The decision as to which drug is the optimal choice for first-line therapy is not always very clear. Each drug has grounds on which it could be considered first-line therapy for diabetic patients.[6] Hence choosing an antidiabetic agent from the available groups is very difficult process for prescribers and is further complicated by variation in sensitivity pattern in different population. It is also necessary to consider the status of rapidly introducing newer agents. In this study we have investigated the prescribing pattern of traditional and newer antidiabetic agents in patients attending the diabetic clinic of a tertiary care teaching hospital.

MATERIALS AND METHODS

This prospective, observational study was conducted for one year in the Diabetic Out Patient department (OPD) in a tertiary care hospital. Patients of all age groups and either sex were included while patients who were unwilling to give information and those suffering from type 1 diabetes mellitus were excluded from the study.

A total of 290 randomly selected patients of type 2 diabetes mellitus were observed during the study period. All the patients who have been prescribed newer oral antidiabetic agents were enrolled while random sampling has been done to enroll the patients receiving traditional oral antidiabetic agents. Personal details, medical history, examination details, complications, investigations done, treatment given, and complications were recorded on each visit on a predesigned case record form. Necessary details of the prescribed antidiabetic drug(s) and other associated medications were also noted. It has been usual practice in present clinic to keep the FBS at or around 120 mg% and PPBS at or around 150 mg% to avoid the occurrence of hypoglycemia and hence forth the same level has been adopted for achieving satisfactory blood sugar level.

RESULTS

A total number of 290 patients suffering from type 2 diabetes mellitus were studied. Out of these, 146 (50.34%) patients were suffering for ≤ 5 years while the remaining for more than that. Mean age of the studied patients was 56.09 years. Males were 142 in number and females 148. Fasting blood sugar (FBS) of 48 patients (22.42%) was ≤ 120 mg% and 132 patients (61.68%) it was more. Post-prandial blood sugar (PPBS) was ≤ 150mg% in 21 patients (9.81%) while in 187 patients (87.38%) it was more. FBS and/or PPBS could not be done in 76 patients (26.21%). About 15% patients were suffering from diabetes related complication. Distribution of patients according to the antidiabetic medications is given in table 1.

Out of 242 patients receiving oral antidiabetic agents, 41 patients (14.14%) received glipizide alone while only 2 patients (0.69%) were receiving metformin alone. The most commonly used combination was glipizide and metformin.

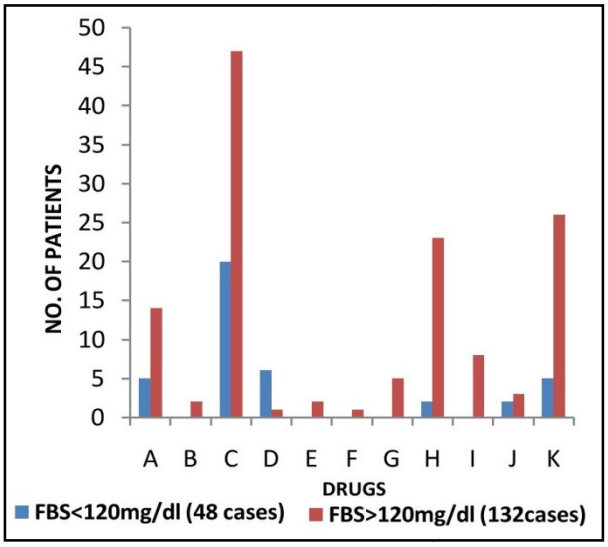
Table-1: Distribution of Patients According to Antidiabetic Medications

Medication		Number of Patients (%)
Oral Antidiabetic Drugs	Single	43 (14.83%)
	Combination	199 (68.82%)
Insulin in Combination with Oral Antidiabetic Drugs		48 (16.55%)
Total		290

Table-2: Distribution Oral Antidiabetic Drugs Prescribed in Combination

Oral Antidiabetic Drugs in Combination	Number of Patients (%)
Glipizide + Metformin	112 (38.42%)
Glipizide + Metformin + Pioglitazone	44 (15.17%)
Metformin + Glimepiride + Pioglitazone	10 (3.45%)
Glipizide + Pioglitazone	8 (2.76%)
Metformin + Glimepiride	8 (2.76%)
Metformin + Pioglitazone	4 (1.38%)
Acarbose + Glipizide + Metformin	4 (1.38%)
Gliclazide + Pioglitazone	4 (1.38%)
Others (Glipizide + Repaglinide; Glipizide + Rosiglitazone; Glipizide + Metformin + Pioglitazone + Glimepiride; Glipizide + Glimepiride)	5 (1.72%)

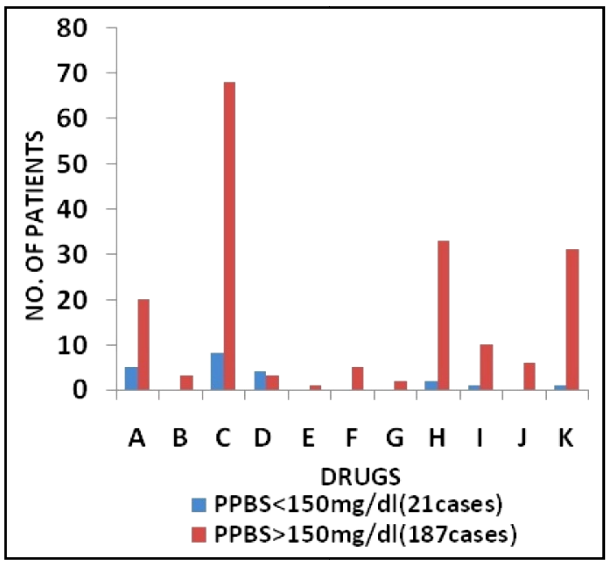
Figure-1: Antidiabetic Medications According to FBS Level



A: Glipizide; B: Metformin; C: Glipizide + Metformin; D: Glipizide + Pioglitazone; E: Metformin + Pioglitazone; F: Glipizide + Glimepiride; G: Metformin + Glimepiride; H: Glipizide + Metformin + Pioglitazone; I: Metformin + Glimepiride + Pioglitazone; J: Other Antidiabetic Combinations; K: Insulin + Oral Antidiabetic Drugs

Among newer agents, pioglitazone, a thiazolidinedione (TZD) was most commonly prescribed agent although in combination with other drugs in 71 patients (24.48%). Insulin was prescribed in 48 patients (16.55%) in combination with oral antidiabetic drugs like glipizide, metformin and pioglitazone. Details of oral antidiabetic agents prescribed in combination are mentioned in table 2. Medication prescribed as per FBS/PPBS levels is shown in figure 1 and 2.

Figure-2: Antidiabetic Medications According to PPBS Level



A: Glipizide; B: Metformin; C: Glipizide + Metformin; D: Glipizide + Pioglitazone; E: Metformin + Pioglitazone; F: Glipizide + Glimepiride; G: Metformin + Glimepiride; H: Glipizide + Metformin + Pioglitazone; I: Metformin + Glimepiride + Pioglitazone; J: Other Antidiabetic Combinations; K: Insulin + Oral Antidiabetic Drugs

The number of antidiabetic drugs prescribed in relation to the duration of disease was studied and it clearly depicts that it increases with the duration of disease. Patients who had diabetes for five years or less could be managed with single oral agent while two or three agents were required in patients having diabetes for more than this period.

DISCUSSION

Diabetes mellitus (DM), a lifelong disorder, comprises a group of common metabolic abnormalities that share the phenotype of hyperglycemia.[7] Insulin resistance and β-cell dysfunction both play important roles in the development and progression of type 2 diabetes.[8] The primary goal in the management of diabetes is to maintain blood sugar level as close to normal as possible.[9] Though non-pharmacological measures are as important as drug therapy, pharmacotherapy represents the mainstay of management of diabetes. Various

pharmacological approaches are used to control blood sugar level via different modes of action: sulfonylureas essentially stimulate insulin secretion; biguanides act by promoting glucose utilization and reduce hepatic glucose production and alpha-glucosidase inhibitors slow down carbohydrate absorption from the gut.[10] Insulin therapy is reserved for advanced stages of the disease when multiple oral treatment fails. Recently several newer classes of drugs with different pharmacodynamic profiles have been approved to achieve better glycemic control. Thiazolidinediones (Pioglitazone), also known as insulin sensitizers, enhances the action of insulin mainly by promoting glucose utilization in peripheral tissues and suppressing hepatic gluconeogenesis.[11] Glimepiride, a sulfonylurea derivative, stimulates insulin release from pancreas and offers several distinct advantages over other drugs of that class. These include rapid onset of action, favorable pharmacokinetic properties, fewer effects on cardiovascular variables and lesser incidence of hypoglycemia.[12]

The present study conducted at a tertiary care hospital has shown that adequate management of diabetes mellitus is difficult to be achieved with a single oral agent. Most of the patients require two or more drugs to achieve glycemic control. The most possible reason for this is that type 2 DM is a chronic disease with a progressive deterioration in glycemic control due to the continuing loss of β-cell function and hence forth monotherapy for type 2 diabetes may therefore not be sufficient to maintain glycemic control over time.[8] It has also been stated that early, aggressive control of glucose level with combination therapy may be able to slow the decline in glycemic control, compared with monotherapy, and reduce the complications of diabetes.[8] The advantages of combination therapy are that drugs with complementary modes of action can target both the underlying insulin resistance and β-cell dysfunction.[8] Prescribers usually prefer a combination of glipizide and metformin. Previous studies also suggested that the most common combined therapy associates sulfonylureas with metformin.[13,14] It has been demonstrated that both the compounds have an additive antihyperglycemic effect, without increasing the adverse effects of either pharmacological class.[10] The conventional approach in our clinic has been to start the treatment with a single well known second generation sulfonylurea drug (for example glipizide). If found inadequate, metformin usually added as a second agent. At times metformin monotherapy is preferred in obese patients while sulfonylureas are prescribed in non-obese or slightly overweight individuals.[15-19] The choice of a sulfonylureas agent is considered to be wise as they are effective both as monotherapy and in combination with agents that have different mechanisms of antihyperglycemic action.[20] However if the results were inadequate prescribers have added one of the newer agents (pioglitazone or glimepiride). In a number of difficult cases, three or four drugs have been used of which one or two were newer agents. As a last resort, insulin is also added to the regimen and one of the oral drugs may be withdrawn. This has also been a generally accepted management plan for the type 2 diabetes elsewhere.[21] Pioglitazone, a thiazolidinedione (TZD) has been the commonest newer antidiabetic agent in use. TZDs improve insulin sensitivity and enhance glucose utilization by adipocytes and skeletal muscles.[22-25] There is now considerable research to suggest, that beyond reducing insulin resistance and providing durable glycemic control, the TZDs exert a number of pleiotropic effects that may play an important role in the treatment of type 2 diabetes mellitus.[8] Number of studies comparing TZDs with sulfonylureas or metformin has demonstrated similar decreases in Hb_{A1c} after 1 year of treatment, the TZDs appear better able to sustain glycemic control in the long term.[8] Both rosiglitazone and pioglitazone have been shown to slow the rate of loss of β-cell function and improve insulin sensitivity to a greater extent than other currently used oral agents.[8] However amongst several TZDs, pioglitazone seems to have been especially favored drug as it may additionally influence the lipid metabolism favorably and has less frequent incidence of hepatotoxicity.[26]

Pioglitazone is also a much cheaper drug in this group.[27] It has been noted that pioglitazone was never used alone. It was used either in combination with sulfonylurea or biguanides or even more frequently with both of these. It has been observed that TZD metformin combination has a powerful effect on reducing insulin resistance and is effective in the early stages of type 2 diabetes when more endogenous insulin is still available. This combination is also associated with minimal hypoglycemia and less weight gain. A sulfonylurea-TZD combination offers the added benefit of lowered insulin resistance and potential improvement in β-cell function.[8] A wealth of short- and long-term studies and literature reviews attest to the fact that the combined use of TZDs with agents such as metformin or sulfonylureas provides better glycemic control compared with further intensifying the metformin or sulfonylurea monotherapy.[8] Inspite of all these, pioglitazone was less prescribed in comparison to sulfonylureas or biguanides. One of the reason for this prescribing trend can be newer oral antidiabetic agents like pioglitazone, glimepiride were not available in government supply (at the time of study period) and they are costly too in comparison to cheaper as well as government supplied antidiabetic agents like glipizide and metformin. Periodic liver function tests are recommended with TZD use and may introduce additional cost for treatment.[6] This factor may have been accounted for while choosing an antidiabetic agent for a particular subset of patients. On the other hand it is also true that long term outcome studies with thiazolidinediones were not available at the time of study period. Moreover they may produce weight gain and edema which have precluded their widespread use in patients with heart failure.[20] Finally, one confounding factor that may have had an impact on the lower utilization of TZDs overall, was the concern with troglitazone, another TZD.[6]

It has been also observed that the number of drugs used in patients of type 2 diabetes increases in proportion with the duration of the disease. Most patients where duration of the disease was five years or less have been managed with single drug. However it seems that a secondary failure and/or resistance may start setting in by this time with the result that two drugs have been required in those having disease for last seven years and three drugs in those having the disease for last eight years. It has been further observed that although two or more drugs including newer antidiabetics and insulin were being used in 116 out of 180 patients, the fasting blood sugar was still inadequately controlled. Similarly out of 208 patients in whom PPBS was estimated, 159 patients have not achieved satisfactory glycemic control. It has been observed that insulin has been added when satisfactory blood sugar level has not been achieved after combined oral therapy and in patients having diabetic complications. Yki-Jarvinen H[28] has also noted that in type II diabetes, insulin is often used after other treatments have failed. Some authors, recognizing the multi-drug oral combinations are not particularly effective, have suggested that insulin is underused.[28] There can be many limitations for starting insulin therapy and especially economical aspect can be the most plausible reason for this study patients.

Present study has several limitations. Socio-economical analysis of the patients was not done and hence it is difficult to predict up to which extent pharmacoeconomical factor was responsible for this prescription pattern. Follow up of these patients were not possible and hence efficacy of the prescribing agents have not been done. Further studies should be required on a larger number of study patients with subsequent follow up to decide the real effectiveness of newer agents.

CONCLUSION

We conclude that although a combination of glipizide and metformin has been most frequently prescribed, it has not been sufficient to achieve adequate glycemic control especially in patients having diabetes for more than five years. Several patients required three or more oral antidiabetic agents and a combination with insulin. Newer antidiabetic agents have been

prescribed in combination. Pioglitazone has been the most frequently prescribed medication in combination with glipizide and metformin. Even with all these medications a tight glycemic control is achieved in very few patients which needs an attention.

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Cite this article as: Dave DJ, Dikshit RK, Gandhi AM. Utilization of some newer oral antidiabetic agents in a tertiary care hospital. Natl J Physiol Pharm Pharmacol 2012; 2:146-151.
Source of Support: Nil
Conflict of interest: None declared