DRUG UTILIZATION PATTERN AND EFFECTIVENESS ANALYSIS IN DIABETES MELLITUS AT A TERTIARY CARE CENTRE IN EASTERN NEPAL

PREMLATA DAS[1]*, BALBHADRA PRASAD DAS[1],
GAJENDRA PRASAD RAUNIAR[1],
RANENDRA KUMAR ROY[1] AND
SANJIB KUMAR SHARMA[2]

Department of [1]Clinical Pharmacology and Therapeutics and [2]Internal Medicine,
B. P. Koirala Institute of Health Sciences,
Dharan, Nepal

Abstract : An observational follow up study conducted for one year at a tertiary care centre in 154 newly diagnosed diabetes mellitus patients is presented. The aims of the study were to determine the demographics, prescribing patterns, drug cost and analyze effectiveness of different therapies. Effectiveness of therapies were analyzed in patients achieving glycemic control by Wilcoxon signed- rank test. Majority of patients (n = 114) fell into the middle age strata of 35-64 years and 97% were type 2 diabetics. A total of 282 prescriptions were screened that included antidiabetics and other drug categories. Mean number of drugs per prescription sheet was 1.83±1.31. Oral hypoglycemic agents were advised to 64% of the patients. The prescribing frequency of biguanides (24.5 %) was more than sulphonylureas (19.9 %). Only 67 patients followed up for 3 months±15 days, of which 46 achieved glycemic control. The biguanides only group (p=0.002) and combination therapy of biguanides and sulphonylureas group (p=0.005) were the highly effective therapies, as their p values of fasting blood glucose levels on follow up were the lowest. Nearly 90% of patients on combination therapy achieved glycemic control. In conclusion, this study reflects the therapeutic approach followed in diabetes mellitus as optimal. Future research on a larger patient population is warranted to evaluate existing patterns of therapy for sound practice and quality of care.

Key words : diabetes mellitus   drug utilization   Nepal

INTRODUCTION

Drug utilization research is an eclectic collection of descriptive and analytical methods for the quantification, understanding and evaluation of the processes of prescribing, dispensing, and consumption of medicines, and for the testing of

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*Corresponding Author : Dr. Premlata Das, Assistant Professor, Department of Clinical Pharmacology and Therapeutics, B. P. Koirala Institute of Health Sciences, Dharan, Nepal; Email id: premlatadas@yahoo.com

interventions to enhance the quality of these processes (1). They are powerful exploratory tools to assess whether drug therapy is rational or not and for creating a sound socio-medical and economic basis for healthcare decision making (2, 3). This kind of research into diabetes mellitus (DM) will provide useful insights into the different therapeutic traditions, reflect disease prevalence and data can be linked to measures of morbidity in order to explore efficacy and toxicity of different therapies (4, 5, 6). Drug utilization review combined with elements of disease management expands the focus from only drug-specific problems to an approach that also uses treatment guidelines and algorithms to evaluate the appropriateness of drug therapy in the context of treating particular diseases. This requires consideration of health outcomes and pharmacoeconomic findings (7). Applying the framework of economics in diabetes prevention and control is important because the need for resources will continue to increase due to the increasing burden of the disease and demand for comprehensive care and newer treatments (8). Literature review of these studies in Nepal is scarce (9, 10). Hence this study was undertaken in eastern Nepal with the following objectives : 1. to describe demographic details (sex distribution, age, diagnoses) of diabetic patients under study, 2. to study the type of initial therapy in type 2 DM patients in the form of :- diet only; diet and oral antidiabetics; diet, oral antidiabetics and insulin, 3. to evaluate drug utilization pattern in diabetic outpatients, and 4. to analyze effectiveness of different existing drug therapies and obtain cost-effectiveness of the most effective therapy.

MATERIAL AND METHODS

The study was conducted at B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal, a tertiary healthcare centre. It was an observational follow up study, carried out from July 2007 to June 2008 in patients visiting the diabetic outpatient clinic of the Internal Medicine department. The study protocol was approved by the Institutional review board of BPKIHS.

Eligible patients were newly detected cases of diabetes, diagnosed within a span of three months or less. The criteria followed for diagnosis was as set by WHO (11). A structured proforma was used to collect information from the patients' prescription sheets and laboratory investigation reports after consultation. Patients were followed up for a period of 3 months±15 days.

Effectiveness of drug therapy for different treatment regimens was evaluated in follow up cases achieving glycemic control i.e. Fasting Blood Glucose (FBG) < 130 mg/dl (12). This was done from FBG values obtained at time of diagnosis (FBG I) and at the end of 3 months±15 days (FBG II) for each patient by analyzing them statistically by Wilcoxon signed-rank test. The most effective treatment group considered was the one in which maximum number of patients achieved glycemic control.

Costs of drugs were obtained from the Current Index of Medical Specialties (CIMS), Jan-April 2010 [Update 1] (13). Drug acquisition costs (cost of buying a drug) were calculated using the cost of the cheapest available preparation and for the most

commonly prescribed dose after converting into Nepalese currency. For the prescribed oral antidiabetic drugs, cost price was determined on a daily basis and then for a period of 3 months.

Cost effectiveness analysis was done by obtaining incremental cost-effectiveness ratio (ICER) for a period of 3 months. This ratio assesses the net incremental cost of gaining an incremental health benefit over another therapy (2). In this study comparison was made between the two most effective treatment modalities.

ICER was obtained using the following formula :

Incremental Cost-effectiveness ratio (ICER) =

[Cost of Drug A − Cost of Drug B] ÷ [(FBG I_A − FBG II_A) − (FBG I_B − FBG II_B)]

(Where, A = Most effective therapy, B = 2nd most effective therapy).

Data were tabulated and entered in Microsoft Excel. Analysis was done with the help of Statistical Package SPSS. Descriptive analysis of the variables were carried out. Different parameters were compared using Wilcoxon signed- rank test as the test variables were not normally distributed.

RESULTS

A total of 154 newly diagnosed patients of diabetes mellitus were enrolled in the study, out of which 47.4% were males (n=73), and 52.6% were females (n=81). Approximately 74% (n=114) of patients fell in the age group between 35–64 years. The median (IQR) values of age for male patients was 46 (38–54), and that of females was 43 (38–52) years.

Amongst all patients, 5 (3.3%) were diagnosed as type 1 and the remainder were type 2 [n=149 (96.8%)] diabetics. Co-morbidities at the time of diagnosis were found in 59 (38.3%) patients. Hypertension was present in 57 cases (37%), it being the most common co-morbidity followed by dyslipidemia (n=5, 3.3%) and symptomatic coronary artery disease (n=2, 1.3%).

Type II patients received the following treatment regimen: diet only regimen was prescribed to 51 patients (33.1%), while 96 patients (62.3%) were advised diet + oral hypoglycemic agents (OHA). Rest of patients (n=2, 1.3%) were advised diet + OHA + insulin.

A total of 282 prescriptions were screened, of which 142 (50.4%) drugs were antidiabetics. Amongst these, biguanides (metformin) were the most frequently (24.5%) prescribed. A total of 140 drugs of other categories were prescribed. All the drugs were prescribed by brand names. The Mean±SD of drugs per prescription was 1.83±1.31 (range = 1–6 drugs), with 66.9% (n=103) of patients receiving 2 drugs or less. Details on all drugs prescribed are summarized in Table I.

Only 67 (43.5%) patients followed up and data are in relation to their prescription, after a time span of 3 months±15 days since their first visit. Type of therapy in these patients are depicted in Fig. 1. A moderate change in treatment regimen was observed

TABLE I : Prescription pattern of drugs (n=282) in the newly detected diabetic cases at the time of diagnosis.

Drug category		Number of drugs	Percent of total number (n). [%]
Biguanides	Metformin	69	24.5
Sulphonylureas	Glimepiride	53	19.9
	Glipizide	3	
Thiazolidinediones	Pioglitazone	10	3.6
Insulin	Glargine	2	
	Soluble + Isophane insulin	5	2.5
ACE inhibitors		62	21.9
Beta blockers		13	4.6
Calcium channel blockers		12	4.3
Hypolipidemic drugs		12	4.3
Angiotensin II receptor blockers		11	3.9
Diuretics		9	3.2
NSAIDs		9	3.2
Haematinics and Multivitamins		4	1.4
Antimicrobial agents, Proton pump inhibitors, Antidepressants Anticoagulants, Organic nitrates.		8	2.8

in these cases with an increase in combination therapy (Fig. 1).

In the follow up group, 46 (68.7%) patients achieved glycemic control (FBG < 130 mg/dl). Their median values of FBG I was 164
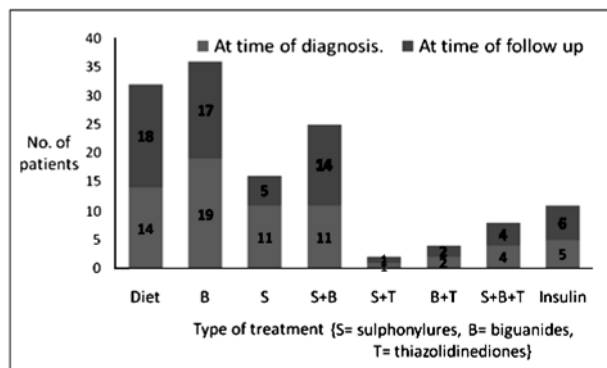

Fig. 1 : Differences in treatment regimen before and after follow up. (No. of patients = 67).

mg/dl and FBG II was 108.5 mg/dl. In the uncontrolled group of 21 patients, median values of FBG I was 216 mg/dl and FBG II was 153 mg/dl. Data in relation to different therapeutic categories are given in Table II.

Analysis for effectiveness of drug therapy was done by Wilcoxon signed-rank test. The P values of FBG levels for biguanides only group was 0.002 and for combination of biguanides + sulphonylureas group was 0.005 which are highly significant (Table II). Therefore it can be concluded that these were the highly effective therapeutic modalities. As the number of patients in other drug group combinations were small, their analysis was not done. Further it can be seen that the combination therapy of metformin and sulphonylurea was the most effective pharmacological treatment regimen among the patients under study, with 90.9% achieving glycemic control followed by biguanides (metformin) only therapy (Table II).

Analysis for cost-effectiveness was as follows :

Incremental cost-effectiveness ratio (ICER) =

[Cost of Drug A – Cost of Drug B] ÷ [(FBG I_A – FBG II_A) – (FBG I_B – FBG II_B)],

[where, A = Metformin + Sulphonylurea combination therapy and, B = Metformin only therapy].

ICER = [353.41–172.80] ÷ [(201–106.5) – (188–110)] = 180.61 ÷ [94.5–78] = 180.61 ÷ 16.5 = 10.95.

Therefore, ICER = Rs. 10.95 per mg/dl

TABLE II : Data on cost and median values of FBG in follow up patients achieving glycemic control in relation to different categories of treatment.

Type of treatment	Total no. of patients (n)	No. of patients with FBG II <130 mg/dl	Cost prices for 3 months therapy (Rs.)	Median (IQR) values of FBG I (mg/dl)	Median (IQR) values of FBG II (mg/dl)	Difference of median values of FBG I & FBG II	P value
Diet	14	12 (85.7%)	------	139.5 (127.75–164.5)	108.5 (94.25–114.5)	31	0.003*
Metformin	19	13 (68.4%)	172.80	188 (129–209)	110 (100–121)	78	0.002*
Sulphonylurea	11	5 (45.5%)	180.61	184 (124.5–233)	108 (85.5–110.5)	76	0.080
Metformin + Sulphonylurea	11	10 (90.9%)	353.41	201 (156.75–250)	106.5 (87.75–120)	94.5	0.005*

*Significant

decrease in blood glucose (i.e. an increased cost of minimum ~ Rs. 11/- is required for every 1 mg/dl decrease in fasting blood glucose levels).

DISCUSSION

A diabetes mellitus epidemic is underway (14). It is a chronic disease requiring lifelong treatment. Although lifestyle changes remain the cornerstone of diabetes management, individually they are often insufficient to enable patients to maintain normal blood glucose levels. Pharmacological therapy therefore forms an integral component in the armamentarium of management of diabetes mellitus (4, 15).

In this study, a significant finding was that ~74% of patients fell in the age group of 35–64 years. This is consistent with data given by WHO, which states that in the developing countries, the most frequently affected are in the middle productive years of their lives (14, 16). With this age group bearing the burden of diabetes, there is a natural adverse effect on the quality of life of the patients and their family members. This may have a major implication in such nations, as the disease is often associated with loss of productivity, causing socio-economic and psychological setbacks.

The average number of drugs per prescription is an important index of the scope for review and educational intervention in prescribing practices. By and large, it is difficult to keep the mean number of drugs per prescription below two, but higher figures always ought to be justified, because of the increased risk of drug interactions and errors of prescribing. Besides polypharmacy is often associated with higher cost, increased side effects and non compliance. In this present study, mean prescribed drugs were below 2 (mean±SD = 1.83±1.31), indicating minimal and rational prescribing practices. Similar results were obtained in a study of diabetic patients in India, where the average number of drugs per prescription was 1.95 (3). A study conducted in Pokhra, Nepal however showed slightly higher values of 3.76 (9).

In this study of DM cases, antidiabetics accounted for 50.4% of all drugs prescribed, with ~64% of patients receiving oral hypoglycemic agents. This is justified by the fact that majority of the patients in this study were type 2 diabetics (96.8%). The prevalence rates of type 2 diabetes is anyways increasing, due to increasing obesity and reduced activity levels (12).

Studies conducted in South Africa, US and India during the late 1990s have reported sulphonylurea as the most frequently prescribed antidiabetic agent (4, 15, 17). However prescribing trends have been changing as reported by more recent studies around the world that show metformin as the most commonly prescribed drug (18, 19, 20). In this study too, biguanides (metformin) was most frequently (n=69) prescribed followed by sulphonylureas (n=56). This pattern is consistent with the current treatment algorithm for type 2 DM from the American Diabetes Association and the European Association for the Study of Diabetes, which suggest that metformin should be started along with lifestyle recommendations at the time of diagnosis (21, 22). Metformin is the best first option at present due to its efficacy, weight reducing effect, cost and low incidence of adverse effects (23). It has an added advantage of improving lipid profile, not provoking hypoglycemia and can be associated with any other antidiabetic agent. (12, 24). Sulphonylureas remain the best choice for combination with metformin although their effectiveness on glucose control decrease with time more rapidly (23).

Increased utilization of other drug categories is significant in diabetes patients.

An important reason is the high incidence of long term complications associated with diabetes (25). Besides many individuals with type 2 DM have complications at the time of diagnosis, attributed to the fact that they are often associated with long asymptomatic phases of hyperglycemia (12). In this study approximately half of the drugs (49.7%) accounted for the other categories. Amongst these, cardiovascular drugs like angiotensin converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers and diuretics were mainly prescribed concurrently. It is well known that there is an increased risk of heart disease in diabetics, with coronary artery disease being the leading cause of death among the patients (15, 25, 26). Hence the increased utilization of cardiovascular drugs is as anticipated. This finding is further supported by the fact that cardiovascular disease was the most common co-morbidity found in the patients at the time of diagnosis, with hypertension being present in ~37% of all cases followed by dyslipidemia. Similar reports were from studies in Nepal, Germany and Belgium (9, 20, 27).

An interesting observation is the high frequency of ACE inhibitors prescription (~22%). Implementation of ACE inhibitor therapy on diagnosis of type 2 diabetes in normoalbuminuric and microalbuminuric patients is a dominant strategy, being more effective and less costly across all outcomes and may also increase survival by prevention of cardiovascular disease events (12, 28). The high prescribing rates of this drug is thus justified. Studies in Trinidad and Tobago over a period of 10 years also show that the proportion of treated patients prescribed ACE inhibitors increased from 8% to 72% (29).

Further analysis of other drugs reveal low prescription rates for beta blockers (4.6%). This could probably be due to the fact documented that beta blockers (especially non-selective) have potential to mask signs and symptoms of hypoglycemia, and hence are best avoided (12, 15). However deterioration in glycemic control or blunted counter-regulatory responses to hypoglycemia are seldom clinically important problems with cardioselective beta-blockers. Beta-blocker underuse is a growing concern, especially in circumstances in which evidence from large trials suggests that these drugs are effective in high-risk patients with diabetes after myocardial infarction, particularly in those with left ventricular dysfunction (12, 25).

Randomized controlled clinical trials traditionally provide information on drug safety and efficacy. However drug utilization patterns and clinical effectiveness in a "real world" setting may differ substantially from the data provided from such trials. Most often, clinical effectiveness is influenced by prescriber agent selection and therapy changes, as well as patient adherence with the drug regimen (4). In this study, combination of biguanides and sulphonylureas was found to be most effective, with glycemic control (FBG < 130 mg/dl) being achieved in ~91% of patients. Similar results were found from a study in Kathmandu, Nepal (10). A surprising observation is that a large percent of patients on diet alone (~85%) achieved glycemic control. This is likely to occur, as the population chosen for diet therapy had less severe hyperglycemia and is consistent with standard clinical practice decisions. However efficacy of diet therapy itself cannot be ruled out.

Many health care providers strive to achieve normalization of blood glucose and achievement of these goals often prompts them to consider combination therapy to target different pathogenic mechanisms and manage both fasting and postprandial blood glucose levels. Besides many patients fail to achieve glycemic goals with initial monotherapy and of those who achieve, few consistently maintain. Thus maintenance of glycemic control over the lifespan of a patient with diabetes is overwhelmingly likely to require combination therapy (30, 31). The prescription pattern at follow up in this study also reveals an increase in combination therapy.

The latest WHO estimate for the number of people with diabetes in Nepal in 2000 was 436,000. This is projected to increase to at least 1,328,000 by 2030 (32). Given the prediction that the prevalence of DM is increasing, the financial implications are stark so cost of drug therapy cannot be overlooked. There is much variation in the cost prices of the drugs in the market. Besides the study here revealed all drugs were prescribed by brand names. Thus, there is a huge scope in reducing the cost prices by prescribing drugs by their generic names, so that cheaper alternatives from pharmacies may be obtained, without a compromise on its quality. Therefore much emphasis is placed on a cost-effective therapy.

This study contributes to the growing body of literature on drug utilization research. Their scope is to evaluate not only trends of drug usage but also appropriateness of prescriptions and adherence to evidence-based recommendations. Information from these drug use measures can also be used

by health planners and prescribers to outline newer guidelines for standard efficient therapy.

Limitations

Glycated hemoglobin (HbA1$_c$) is a more reliable parameter to assess glycemic control over a period of 3 months. However it could not be used in this study because all the patients were new cases, and currently HbA1$_c$ is not considered a suitable diagnostic test for diabetes mellitus (11, 21). As evaluation of effectiveness of drug therapy required comparison between parameters before and after therapy, FBG values were only focused upon. This is a major limitation of this study.

This study was limited to an academic practice, that may differ from community practice settings. Besides the prospective data sample is small and duration of follow up is short. However this study can form a basis for future studies with larger number of patients followed up for a longer duration of time and which will be reflective of a full population. Including compliance check will strengthen the study even more.

Conclusion

The present study has clearly delineated the drug utilization pattern of newly diagnosed diabetic patients at BPKIHS, a tertiary care centre in Eastern Nepal. More than 90% of patients were diagnosed as type 2 DM. High frequency of oral hypoglycemic agents were prescribed, reflecting higher glycemia at the time of diagnosis. Amongst this group of drugs biguanides accounted for the most commonly prescribed drug. Polypharmacy was found to be low, suggestive of more rational mode of prescribing. Besides our data demonstrate the effectiveness of combination therapy in reducing hyperglycemia associated with diabetes mellitus, as compared to monotherapy.

Therefore through a thorough understanding of the existing prescribing patterns, attempts can be made to improve the quality and efficiency of drug therapy. Besides, setting standards and assessing the quality of care through performance review should be a part of everyday clinical practice.

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