Research Article**Drug utilization study of anti-diabetics in elderly diabetic, hypertensive in-patients with or without impaired renal function in a tertiary care hospital****Prasan R. Bhandari^{1*}, Apeksha Bhandary²**¹Associate Professor, Department of Pharmacology, SDM College of Medical Sciences & Hospital, Dharwad, Karnataka, India²Post Graduate, Department of Pharmacology, SDM College of Medical Sciences & Hospital, Dharwad, Karnataka, India

Received: 19 July 2018

Revised: 7 August 2018

Accepted: 22 August 2018

Abstract

Background: Hypertension (HTN) and Diabetes mellitus (DM) are the primary contributors to the renovascular mortality and morbidity. Drug utilisation studies (DUS) are prospective tools in the assessment of health care systems. **Objectives:** To analyse the prescription pattern of anti-microbials in elderly hypertensive diabetic in-patients with or without renal impairment in a tertiary hospital. **Methods:** The study population comprised of 165 hypertensive diabetic in-patients at Shri Dharmasthala Manjunatheshwara (SDM) Hospital. Questionnaire based evaluation was carried out and prescriptions of patient with HTN and DM at and above the age of 60 years irrespective of gender were included. **Results:** Out of 226 anti-diabetic drugs, 193 were single drugs and 33 were FDCs, among the total 123 drugs were used in patients with impaired renal function. There was no significant difference in the number of anti-diabetic drugs used in patients with impaired renal function and in patients with normal renal function, ($p > 0.05$). Out of 193 single drugs, 83.42% ($n=161$) were insulins and 16.58% ($n=32$) were of oral anti-diabetic drugs. Among insulins, intermediate acting insulins were used in majority 63.73% ($n=123$) followed by long acting insulins, 19.69% ($n=38$). Amongst oral antidiabetics drugs, biguanides, with metformin being the most commonly prescribed drug, 9.84% ($n=19$). **Conclusions:** Intermediate acting insulin was the most common class of drug prescribed and combination of glimepiride + metformin was the most common FDC prescribed in patients with or without impaired renal function.

Keywords: Antidiabetic, biguanides, renal impairment, metformin

Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial disorder afflicting multiple organ systems (Jung et al., 2014; Park et al., 2015). It is characterized by the resistance of cells to insulin, leading to hyperglycemia (Ved and Shah, 2012). This disorder is associated with microvascular and macrovascular complications that in the long-term can lead to morbidity and mortality (Valensi et al., 2015; Wang et al., 2013).

It was assessed that in 2017 there are 451 million (age 18–99 years) individuals with diabetes worldwide. These numbers were expected to increase to 693 million by 2045. It is estimated that almost half of all people (49.7%) living with

diabetes are undiagnosed (Cho et al., 2018). The WHO has estimated that maximum growth in number of diabetics would happen in India. With a high genetic tendency and high vulnerability to environmental insults, the Indian population faces a greater risk of diabetes and its associated complications (Ramachandran, 2005.). The number of individuals living with diabetes in India was 31.7 million in 2002, and it is projected that the number will be 79.4 million by 2030 (Gupta et al., 2009; Anon, 1997; Khatib et al., 2008). Bearing in mind the large population and growing prevalence of DM in India, affliction of diabetes in India will be enormous in future years (Ramachandran et al., 2001).

Chronic kidney disease (CKD), defined as either decreased glomerular filtration rate (GFR) or albuminuria, or both, carries a risk of cardiovascular morbidity and mortality and progression to end-stage renal disease. Diabetes and hypertension are major causes of CKD. Therefore, current international guidelines recommend yearly screening for CKD in patients with diabetes or hypertension (Van der Meer et al., 2010).

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DOI: <https://doi.org/10.31024/ajpp.2018.4.6.9>

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CKD was frequently detected in older patients with T2DM, and the progression rate to CKD is also high. Accordingly, it is imperative to detect and manage CKD as timely as possible in elderly patients with T2DM, particularly in those with diabetes period ≥ 10 years (Kim et al., 2018).

Higher risk of chronic illness in elderly increases the chances of taking multiple drugs by elderly people, increases the burden on the kidney for its excretion in a kidney that is already declining due to the ageing process (Dutta, 2015).

It can be a challenge to manage glycemic control in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD), due to both patient and medication issues. Although most antihyperglycemic medications can be used in mild kidney disease, many medications are either not advised or require dose adjustments in more advanced CKD.

Drug utilisation studies holds a vital place in clinical practice since it is the base for creating modifications in the drug dispensing guidelines at local and national levels. The eventual objective of such study is to assist rational drug use. Furthermore, as it supports in developing policies to utilize health resources in the most efficient method, it is mainly required in a developing economy like India where health care burden is borne by the patients. The reference standard for drug utilisation is WHO ATC/DDD (Anatomical Therapeutic Chemical/Defined daily dose) methodology (WHO Collaborating Centre for Drug Statistics Methodology, (2009). Defined daily dose (DDD) is defined by the WHO Collaborating Centre for Drug Statistics and Methodology as the assumed average maintenance adult dose per day for its main indication for each drug and route of administration. The DDD hence is an international unit aiding in international or regional comparisons. Though, DDD does not essentially reveal the recommended or prescribed daily dose (PDD). However, a number of studies have described inconsistencies between DDD and PDD for different groups of drugs (Koristkova et al., 2006; Muller et al., 2006; Duarte-Ramos 2006).

Hence a drug utilization study was conducted to evaluate the drug utilization pattern of antidiabetic medicines during hospital stay and at the time of discharge, cost of antidiabetic drugs and defined daily dose (DDD)/100 bed-days during hospital stay in our setup.

DUS can identify the frequent prescribing errors, their causes, the deviation from the guidelines, and the cost effectiveness. In our present study we intend to:

- Analyse the drug usage pattern of anti-diabetics in elderly hypertensive diabetic in-patients in a tertiary hospital.
- Analyse drug usage pattern of anti-diabetics in elderly hypertensive, diabetic in-patients with renal impairment in a tertiary hospital.

Materials and methods

Study design

It was a prospective, observational study carried out at medicine wards in SDM College of Medical Sciences and Hospital, Karnataka. The study protocol was approved by the Institutional ethics committee (SDMIEC 0401 dated 03/11/2015). All the patients were explained clearly about the nature and purpose of the study in their own language and consent was taken.

Inclusion criteria

Patients of either sex at and above 60 years admitted in the medicine wards diagnosed with HTN and DM and were on treatment with anti-diabetics were included.

Patients whose renal profile (Serum creatinine) is available after their admission to the hospital were included.

Exclusion criteria

- Patients less than 60 years of age.
- Patients diagnosed with HTN or DM but not both.
- Patients whose renal profile data was not available.
- Patient/ relative who were not willing to give their consent or were unable to give consent.
- No sufficient data (age, registration number) were available.
- Patients having emergency/life threatening medical/surgical conditions were excluded.

Sample size

A total of 165 hypertensive and diabetic patients clinically diagnosed as per JNC 7 and American Diabetes Association (ADA) at SDM Medicine wards were enrolled.

Participants and data collection

A questionnaire-based study was conducted at the medicine wards. Prescriptions of clinically diagnosed HTN and DM patients at and above the age of 60 years admitted in the medicine wards were included. The questionnaire consisted patient's demographics like age, gender, marital status, religion and registration number. Patient's diagnosis was made as per JNC 7 and ADA 2015. Renal function tests were obtained and creatinine clearance (Cr. Cl) calculated using Cockcroft-Gault equation. BP recording and BS levels, (Random blood sugar (RBS), fasting blood sugar (FBS), and glycosylated haemoglobin (HbA1c), if done, then the values were noted

Data analysis

Descriptive statistics was applied. Data was analysed by proportion and percentages and comparison done using chi-

square test using Statistical Package for the Social Sciences (SPSS) software version 24.

Results

A total of 165 patients were analyzed for various parameters during the tenure of this study in the Medicine wards of SDM College of Medical Sciences and Hospital, Dharwad. On analysis of the data collected, the following findings were noted:

In this study it was found that, the percentage of male and female patients was 56.97% (n=94) and 43.03% (n=71) (Figure 1).

Figure 1. Gender-wise distribution of study participants

Out of the study population 57 (34.55%) were illiterates, whereas primary education was 17.58% (n=29), high school 18.79% (n=31), secondary education 12.12% (n=20), graduates 15.76% (n=26), postgraduates 1.21% (n=2) (Figure 2).

Figure 2 Education-wise distribution of study participants

Figure 3. Distribution of participants as per socio-economic status

According to Modified B.G. Prasad Classification, majority 64 (38.79%) study participants were of class IV socio-economic status, followed by 45 (27.27%) class II socioeconomic status and very few 4 (2.42%) were of class V socioeconomic class (Figure 3).

In this study majority 77 (46.67%) of patients were from the age group 60-65 years, followed by 45 (27.27%) in the age group of 66-70 age years. Only 8 (4.85%) were more than 80 years old. Average age was 67.34 ± 6.91 years (Figure 4).

In the study population majority 88 (53.33%) of the patients had impaired renal function and 77 (46.67%) of patients had normal renal function (Figure 5).

Among the 165 study population 58 patients medications were not changed after admission and continued the same line of anti-diabetic drugs, whereas 73 patients medications were changed, among which 22 patients another class of anti-diabetics were added (Table 1).

A total of 193 anti-diabetic drugs excluding the FDCs were prescribed for 165 patients. Among this ATC class, A10AC (Insulin and analogues for injection, Intermediate acting)

Figure 4. Age-wise distribution of study participants

Figure 5. Impaired renal function in the study participants

was used in majority 63.73% (123), of which regular human insulin was used more frequently (59.07%), followed by A10AE (Insulin and analogues for injection, long acting) 19.69% (38), out of which insulin glargine was only used (19.69%). Among patients with impaired renal function too class A10AC was frequently used (39.9%) with regular human insulin being most commonly prescribed (37.3%) (Figure 6 and Table 2).

The average PDD/DDD for the most commonly prescribed drugs, regular human insulin and insulin glargine was 0.76 and 0.29 respectively in our study population. PDD/DDD ratio ranged between (0.26 – 1.32), least being for metformin (0.26) and maximum for NPH Insulin 75+ Human Insulin 30 (1.32). The range of PDD/DDD for drugs with impaired renal function was (0.28 – 1.32). For Teneeligiptin no DDD was defined as there is no ATC code given to the drug yet (Table 3).

Figure 6. Anti-diabetic drugs prescribed to the study population

Table 1. Study participants whose anti-diabetic medications were changed after admission

Changed	Changed and Added	Not Changed	Not Changed and Added	Reduced
61	22	58	19	5

Table 2. Anti-diabetic drugs prescribed to the study population

Class/ ATC Classification							Generic Name						
ATC	Total		Impaired Renal Function				Drug name	Total		Impaired Renal Function			
			Yes		No					Yes		No	
	n	%	n	%	n	%		n	%	n	%	n	%
A10AC	123	63.73	77	39.9	46	23.8	A10AC30-NPH Insulin 70 + Human Insulin 30	7	3.63	3	1.6	4	2.1
							A10AC30 - NPH Insulin 75 + Human Insulin 25	2	1.04	2	1.0	0	0.0
							A10AC30-Regular Human Insulin	114	59.07	72	37.3	42	21.8
A10AE	38	19.69	23	11.9	15	7.8	A10AE04-Insulin larginine	38	19.69	23	11.9	15	7.8
A10BA	19	9.84	8	4.1	11	5.7	A10BA02-Metformin	19	9.84	8	4.1	11	5.7
A10BB	5	2.59	3	1.6	2	1.0	A10BB02-Gliclazide	1	0.52	0	0.0	1	0.5
							A10BB12-Glimepiride	4	2.07	3	1.6	1	0.5
A10BG	8	4.15	4	2.1	4	2.1	Teneligliptin	8	4.15	4	2.1	4	2.1
Total	193	100.0	115	59.6	78	40.4	Total	193	100.0	115	59.6	78	40.4

Among the 193 anti-diabetic drugs prescribed, majority of drugs were OD dosing 65 (33.68%), followed by as per sliding scale (A/S/S) 64 (33.16%), thrice daily (TID) dosing 49 (25.39%). The most common route of administration was subcutaneous (SC) route 160 (82.90%), 33(17.10%) of drugs where given by oral route.

A total of 33 anti-diabetic drugs FDCs were prescribed for 165 patients. Among only ATC class A10BD (combination of oral blood glucose lowering drugs) was used 100.0% (33) of which Glimepiride + Metformin was used more frequently (66.67%), followed by Voglibose + Glimepiride + Metformin (18.18%). Among patients with impaired renal function too Glimepiride + Metformin was the commonest drug prescribed (15.12%)(Table 4).

Among the 33 anti-diabetic FDCs prescribed, majority of drugs were OD dosing 31(93.94%), followed by BD dosing 2 (6.06%). Oral route of administration was the only route prescribed for anti-diabetic FDCs (100.00%).

There was no significant difference in the number of drugs used in DM in patients with impaired renal function and normal renal function ($P > 0.05$).

The RBS levels were under control (RBS=101- 200mg/dl) in 80 patients and were not under control (RBS= <100mg/dl or >201mg/dl) in 85 patients. 51 patients among patients with impaired renal function, RBS were not under control. There was no significant difference in patients with RBS not under control among patients with impaired renal function and patients with normal renal function ($P > 0.05$). HbA1C was done in 57 patients. There was no significant difference in HbA1C >6.5% among patients with impaired renal function and patients with normal renal function ($P > 0.05$).

Table 3. Average prescribed drug dose (PDD)/defined drug dose(DDD) of anti-diabetic drugs in the study population.

Antidiabetic drugs	Total	Impaired renal function	
		Yes	No
Gliclazide	1.00	0	1.00
Glimepiride	0.75	0.83	0.50
Insulin Glargine	0.29	0.28	0.31
Metformin	0.26	0.28	0.30
NPH Insulin 70+Human Insulin 30	0.71	0.85	0.63
NPH Insulin 75+Human Insulin 25	1.32	1.32	0.00
Regular Human Insulin	0.76	0.76	0.74
Teneligliptin	-	0	-

Table 4 .Anti-diabetic FDCs prescribed to the study population.

Class/ATC Classification							Generic Name							
ATC Code	Total		Impaired renal function				Drug Name	Total		Impaired renal function				
			Yes		No					Yes		No		
ATC	n	%	n	%	n	%	Drug Name	n	%	n	%	n	%	
A10BD	33	100.0	8	24.2	25	75.8	A10BD-Glimepiride+Metformin+Pioglitazone	2	6.06	1	3.0	1	3.0	
							A10BD-Teneligliptin+Metformin	1	3.03	0	0.0	1	3.0	
							A10BD-Voglibose+Glimepiride+Metformin	6	18.18	1	3.0	5	15.2	
							A10BD02-Gliclazide+Metformin	1	3.03	1	3.0	0	0.0	
							A10BD02-Glimepiride+ Metformin	22	66.67	5	15.2	17	51.5	
							A10BD07-Sitagliptin+Metformin	1	3.03	0	0.0	1	3.0	
Total	33	100.0	8	24.2	25	75.8	Total	33	100.0	8	24.2	25	75.8	

Discussion

This study revealed that more than half, 53.3% (n=88) of patients had impaired renal function and 77 (46.7%) had normal renal function compared to a similar study by Shah et al., 38% (n=19) had impaired renal function and 62% (n=31) had normal renal function, (Shah et al., 2013). suggesting the importance of screening of renal function in hypertensive diabetic patients.

A total of 1521 drugs were prescribed for 165 patients among which 884 (55.6%) of drugs were prescribed in patients with impaired renal function. A significant difference in the total no. of drugs used in patients with impaired renal function and patients with normal renal function was seen, ($P < 0.005$).

Out of 226 anti-diabetic drugs, 193 were single drugs and 33 were FDCs, among the total 123 drugs were used in patients with impaired renal function. There was no significant difference in the no. of anti-diabetic drugs used in patients with impaired renal function and in patients with normal renal function, ($P > 0.05$).

Out of 193 single drugs, 83.42% (n=161) were insulins and 16.58% (n=32) were of oral anti-diabetic drugs. Among insulins, intermediate acting insulins were used in majority 63.73% (n=123) followed by long acting insulins, 19.69% (n=38). Amongst oral antidiabetics drugs, biguanides, with metformin being the most commonly prescribed drug, 9.84% (n=19). In impaired renal function patients, a total of 115 (59.6%) anti- diabetic drugs were prescribed, intermediate acting insulins was repeatedly used, 39.9% (n=77) followed by long acting insulins 11.9% (n=23). Oral antidiabetics drugs were infrequently prescribed, 7.8% (n=15). Among oral anti-diabetics metformin was most commonly prescribed 4.1%, (n=8) but was less frequently prescribed in comparison to patients with normal renal function 5.7% (n=11). In contrast to study conducted by Hussain et al., where 71.18% (n=79) were oral and parenteral insulin injection amounted to 28.83% (n=32) (Hussain et al., 2014). Our study consisted of more parenteral insulin

injection. This deviation in prescribing may be due to the study population. Their study included only diabetic hypertensive patients whereas our study had diabetic hypertensive patients with and without impaired renal function.

The PDD/DDD ratio ranged between (0.26 – 1.32). The range of PDD/DDD for drugs with impaired renal function was (0.28 – 1.32), least being for metformin in both patients with or without impaired renal function. This may be due to increased risk of hypertensive diabetic patients for renal damage, and since metformin is contraindicated in patients with impaired renal function due to the risk of lactic acidosis, (Kennedy, 2015). Its dose is lower than the DDD for metformin. Among 33 anti-diabetic FDCs prescribed the most commonly 66.67% (n=22) prescribed drug was Glimepiride+ metformin followed by glimepiride+ metformin+ voglibose, 18.18% (n=6). This is similar to the study conducted by Pandey et al. (2014) where glimepiride + metformin was the most commonly prescribed FDCs (Pandey et al., 2014). Among patients with impaired renal function a total of 8 (24.2%) FDCs were prescribed, which was fewer in number when compared to that of patients with normal kidney function, where 25 (75.8%) FDCs were prescribed. In another study by Santra et al. (2015) on patients with CKD, insulin preferably short-acting insulin was prescribed in 76% patients and oral anti-diabetic agents in 24% patients. Sulfonylureas, biguanides, and gliptins were used individually or in combinations to manage diabetes in CKD Stage I to III patients and in others who were unwilling to take insulin (Santra et al., 2015).

Globally, approximately 200 million people suffer from chronic kidney disease (CKD), frequent etiologies being hypertension, arteriosclerosis, and diabetes. An estimated 40% of patients with diabetes progress to CKD and rigorous blood glucose control by pharmacological intervention can defer CKD progression. Conventional treatment of type 2 diabetes mellitus comprise metformin, sulfonylureas, meglitinides, thiazolidinediones, and insulin. Though these drugs have a significant role in the control of type 2 diabetes, only the thiazolidinedione pioglitazone can be used across the spectrum of CKD (stages 2-5) and without dose adjustment. Newer agents like dipeptidyl peptidase-IV inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors, are progressively being utilized in the management of type 2 diabetes. Nevertheless, a foremost consideration is whether these newer drugs can also be used safely and effectively across the range of renal impairment (Di Lullo et al., 2017).

Because of both patient and medication issues, it can be a challenge to manage glycemic control in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). While most antihyperglycemic agents could be used in mild renal impairment, several drugs are either not recommended or

necessitate dose modifications in more progressive CKD. Newer agents have considerably more data available compared to the older agents as per their use in CKD, however extensive clinical support is still deficient for some drugs. As CKD progresses, dose alteration is necessary for many agents [numerous dipeptidyl peptidase-4 inhibitors, some insulins, sodium glucose co-transporter 2 (SGLT2) inhibitors], however not for others (thiazolidinediones, meglitinides). Certain medications are not suggested for use in more advanced CKD (metformin, SGLT2 inhibitors, some glucagon-like protein-1 receptor agonists) for safety or efficacy reasons. However, there is not always good association between label recommendations, pharmacokinetic or clinical studies, and guideline recommendations for use of these drugs in CKD. Specifically, controversy remains regards the utilization of metformin in moderate CKD and proper use of liraglutide and sulfonylureas in advanced CKD (Roussel et al., 2015).

Pharmacokinetic studies revealed that total exposure to the drug is enhanced in proportion to the reduction of GFR, necessitating recommendations for applicable dose diminutions as per the severity of CKD. Linagliptin is eliminated primarily by hepatobiliary route. Pharmacokinetic study demonstrated only minimal influence of reduced GFR on total exposure, no dose adjustment of linagliptin is required in the case of CKD. The experience with GLP-1 receptor agonists in patients with CKD is inadequate. Exenatide is excreted by renal mechanisms and should not be administered in patients with severe CKD. Liraglutide is not eliminated by the kidney, however should be administered with caution due to limited experience in patients with CKD. Similarly, there are limited pharmacokinetic documentation for lixisenatide, exenatide long-acting release (LAR) and other once-weekly GLP-1 receptor agonists in present development. Numerous case reports of acute renal failure have been mentioned with GLP-1 receptor agonists, possibly because of dehydration resulting from gastrointestinal adverse events. Nonetheless, increasing GLP-1 could also exert favourable renal effects that may contribute to decreasing the risk of diabetic nephropathy (Scheen 2015).

Dipeptidyl peptidase-IV inhibitors can be used in all stages of renal impairment, with appropriate dose reduction, with the exception of linagliptin, which can be used without dose adjustment. No dose adjustment is required for liraglutide, albiglutide, and dulaglutide in CKD stages 2 and 3, although all glucagon-like peptide-1 receptor agonists are currently contraindicated in stages 4 and 5 CKD. At stage 3 CKD or greater, the sodium-glucose cotransporter-2

inhibitors (dapagliflozin, canagliflozin, and empagliflozin) either require dose adjustment or are contraindicated. Ongoing trials, such as CARMELINA, MARLINA, CREDENCE, and CANVAS-R, will help determine the position of these new therapy classes and if they have renoprotective effects in patients with CKD (Davies et al., 2016; Agrawal et al., 2015).

Conclusion

The therapeutic strategy for T2DM in older patients should consider CKD, which is a major prognostic factor. However, it is not easy to prevent the progression to CKD in such patients because they are exposed to polypharmacy to control their comorbidities. The problems of polypharmacy are overdosing caused by drug-drug interaction or reduced clearance of drugs. In this study, so many older patients with T2DM had renal impairment; hence it is imperative to pay attention to their renal function. It is very important for physicians not only to monitor the renal function regularly and adjust the dose of drugs but also to prevent worsening of renal function when they manage older diabetic patients with CKD, especially in those who had diabetes longer than 10 years.

Considerable variability exists with respect to recommendations and clinical data for the many antihyperglycemic drugs used in patients with T2DM and CKD.

Limitations of study

- The study sample was not large and representative of the Indian population. Therefore, the results should be interpreted with caution.
- We did not compare older patients with younger patients. Nevertheless, this study might be valuable in presenting the finding that CKD was commonly observed in older patients with T2DM and that the progression rate to CKD was also high compared to the general population.
- Since this study included only the Indian population, the results cannot be applied directly to other populations.
- Finally, we could not analyze and reflect HbA1c variability and medication change.
- Large-scale prospective study would be warranted.

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