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Research Article

ANTIHYPERTENSIVE DRUG USE IN PATIENTS HAVING COMORBID DIABETES: CROSS SECTIONAL PRESCRIPTION PATTERN STUDY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: Hypertension and diabetes when present together are associated with a multitude of complications, all of which result in increased morbidity and mortality. This makes it vital to, not only make an early detection of the disease, but also to make the best use amongst the wide array of drugs available for treatment. This study aims at analyzing the influence of current guidelines on prescribing in this particular subset of patients.
Methods: Case history of patients having hypertension along with diabetes was noted down from the medical records department. Diabetes was further sub classified into those who had and did not have nephropathy. Drugs prescribed in each of these groups were noted and pattern analyzed. A total of 128 prescriptions were of diabetes, amongst which 19 had nephropathy and the remaining 109 did not have nephropathy.
Results and Conclusions: The CCB's were the group of drugs prescribed the most in both diabetes and diabetes associated nephropathy. They were prescribed in 60% patients with diabetes, and 95% of those who had nephropathy. The ACE-inhibitors and ARB's were prescribed in 45% patients with diabetes and 21% in diabetes associated nephropathy. Utilization of ACE- inhibitors is thus well below it is expected to be in both diabetes as well as diabetes associated nephropathy.

Keywords: Antihypertensives, Prescription pattern, Diabetes, Diabetic nephropathy Joint National Committee Guidelines,Pharmacoepidemiological study

INTRODUCTION

Persons with hypertension have a high prevalence of insulin resistance and are increasingly predisposed to developing type 2 diabetes mellitus. Moreover, prevalence of hypertension is 1.5 to 2 times greater in patients with diabetes mellitus compared with matched non diabetic individuals [1]. Hypertension and diabetes are thus closely interlinked and, to an extent, can be seen as a cause and effect of each other. The coexistence of diabetes mellitus and hypertension is also important as they are multiplicative risk factors for macrovascular and microvascular disease, resulting in increased risks of cardiac death, coronary heart disease, congestive heart failure, cerebrovascular disease and peripheral vascular disease. Macrovascular complications (coronary artery disease, cerebrovascular disease or peripheral vascular disease) account for majority of deaths in the diabetic population and the absence of hypertension is associated with long term survival.

The incidence of stroke among patients is upto 3 times that in the general population [2]. Microvascular disease resulting in diabetic nephropathy, retinopathy and neuropathy leads to significant morbidity and mortality. Hypertension can contribute to as much as 75 % of all diabetes mellitus related complications, including nephropathy and end stage renal disease. The progressive decline in glomerular function that is seen in diabetic patients with hypertension, especially those with albuminuria can be slowed with antihypertensive treatment .The Joint National Committee (JNC) on detection, evaluation and treatment of blood pressure has published reports outlining recommendations and guidelines in the treatment of hypertension , including those patients having comorbid diabetes. The sixth and seventh report of the JNC is based on significant available clinical data that establish the utility of certain major classes of antihypertensives for the treatment of a variety of comorbidities.The Indian guidelines for the treatment of hypertension, endorsed by the Cardiology Society of India, The Hypertension Society of India and the Indian College of Physicians closely follow the JNC6 and JNC 7 guidelines. This study aims at observing the pattern of utilization of different groups of antihypertensives in patients having hypertension with comorbid diabetes in a tertiary care hospital, reviewing the pharmacological basis for the current guidelines and correlating the data obtained from the study to these guidelines.

METHODS

Kasturba Hospital, Manipal is a premier healthcare institution providing tertiary care to both domestic and international patients.

The hospital is attached to Kasturba Medical College, having a capacity of 1475 beds. The hospital has 15 specialty and 15 super specialty departments. Kasturba Hospital also maintains an elaborate medical records department where patient information is updated on a regular basis.

At the beginning of the study, a protocol was presented before the ethical committee comprising of seven members, and approval for conducting the study was obtained.

The focal point of collection of the data was the Kasturba hospital Pharmacy. Prescriptions that were being brought at the pharmacy were screened over a four month period. Amongst all the prescriptions that were screened, only those prescriptions that had antihypertensive medication as a component were noted along with the hospital number. Corresponding to the hospital number, the medical files of the requisite patients were obtained from the medical records department. A total of 303 prescriptions were thus obtained. Subsequently, a detailed profile of each of the patients was made in terms of demographic characteristics as well as the specific clinical condition for which the antihypertensives were prescribed. Only those patients having hypertension as the primary disease and diabetes as the secondary comorbid condition were included in the study. Based on the detailed patient information obtained from the medical records, diabetes was further sub classified into those who had and did not have coexisting nephropathy. A total of 128 prescriptions were included in the study. The different groups of antihypertensives prescribed in each one of these subset of patients were noted and the results thus obtained were analyzed.

Table 3: Relative use of antihypertensives in males and females

	Males	Females
	n(%)= 84(%)	n(%)= 44(%)
CCB's	53(63%)	30(68.2%)
Beta-blockers	28(33.3%)	15(34%)
ACE-I/AT2RB	33(39.3%)	20(45.5%)
Diuretics	26(31%)	11(25%)
Clonidine	12(14.3%)	02(4.5%)
Prazocin	04 (4.8%)	03(6.8%)

Table 1: Antihypertensive drug use in diabetes with andwithout nephropathy

Antihypertensive drug class	Drug	Diabetes without nephropathy	Diabetes with nephropathy
		109 (85.2%)	**19 (14.8%)**
Calcium channel blockers	Amlodipine	53	14
	Diltiazem	08	04
	Nifedipine	03	0
	Verapamil	01	0
Total : 83 (64.8%)		**65 (59.6%)**	**18 (94.7%)**
Beta blockers	Metoprolol	10	01
	Carvedilol	08	02
	Nebivolol	03	01
	Atenolol	16	02
Total : 43 (33.6%)		**37 (33.9%)**	**06 (31.5%)**
ACE-I/AT2RB	Ramipril	16	02
	Enalapril	13	0
	Lisinopril	10	0
	Losartan	09	02
	Telmisartan	01	0
Total: 53 (41.4%)		**49 (45%)**	**04 (21%)**
Diuretics	Thiazides	07	02
	Frusemide	10	12
	Spironolactone	0	03
	Amiloride	03	0
Total : 37 (28.9%)		**20 (18.3%)**	**17 (89.4%)**
Miscellaneous drugs	Clonidine	09	05
	Prazocin	06	01
Total: 21 (16.4%)		**15 (13.8%)**	**06 (31.5%)**

Table 2: Comparative use of monotherapy and combination therapy

	N (%)	Diabetes without nephropathy	Diabetes with nephropathy
	n=128	**n=109**	**n=19**
Monotherapy	**57 (44.5%)**	**54(49.5%)**	**03(15.8%)**
Calcium channel blockers	25 (19.5%)	23(21.1%)	02(10.5%)
Beta blockers	11 (8.6%)	11(10%)	0
ACE-I/AT2RB	18 (14%)	18(16.5%)	0
Prazocin	01 (0.8%)	01(0.9%)	0
Clonidine	02 (1.6%)	01 (0.9%)	01(5.2%)
Combination therapy	**71 (55.5 %)**	**55(50.5%)**	**16(84.2%)**
Two -drug combination	35 (27.3%)	29(26.6%)	06(31.8%)
Three- drug combination	31(24.2%)	25(22.9%)	06(31.8%)
Four- drug combination	05 (3.9%)	01 (0.9%)	04(21%)

RESULTS

Amongst all hypertensive diabetics, nephropathy was present in 14.8% of the patients. The remaining 85.2% patients were diabetic but had no nephropathy. The overall use of antihypertensives in diabetes is shown in table 1.The utilization of the calcium channel blockers supersedes all other groups of antihypertensives in diabetes with and without nephropathy. Use of the calcium channel blockers is around 60% in patients without nephropathy which increases to almost 95% in patients having nephropathy. Amlodipine is the predominantly used CCB in both groups. The ACE-Inhibitors/AT2RB's is the antihypertensive class used the most following the CCB's. Use is 45% in diabetics which reduces to 21% in associated nephropathy. The overall use is around 41%. The use of diuretics in diabetes is 18% which increases to almost 90% in patients with nephropathy. The loop diuretic frusemide is the most commonly prescribed diuretic in diabetes with and without nephropathy.

Table 2 shows the relative use of monotherapy and combination therapy. A combination of two or more drugs has been used more frequently (55.5%) than the use of a single drug (44.5%). The use of monotherapy reduces from around 50% in those without nephropathy to around 16% in those having nephropathy. The use of combination therapy increases from 51% in those without nephropathy to 84% in those having nephropathy.

Table 3 shows the relative use of antihypertensives in both genders. Marked gender based differences have not been found to be there between the two groups of diabetes.

DISCUSSION

Clinical trials indicate that more than 65% of patients with diabetes and hypertension will require 2 or more different antihypertensives to achieve the target blood pressure of less than 130/80 mm Hg [3,4,5] .The different antihypertensive groups preferred include the ACE inhibitors, alpha blockers, calcium channel blockers and diuretics in low doses because of fewer adverse effects on glucose homeostasis, lipid profiles and renal function [6,3] . ACE inhibitor therapy, according to the guidelines, should be an integral component of any antihypertensive regime in patients with diabetes. These agents have demonstrated a significant role in reducing coronary vascular disease [7,8] and renal disease [9]. This can be attributed to the various metabolic and renoprotective effects of the ACE-Inhibitors. ACE inhibitors block the enzymatic breakdown of bradykinin, enhancing its vasodilatory action [10] which in turn increases blood flow in skeletal muscles. This facilitates an increase in glucose delivery to these insulin sensitive tissues. Bradykinin has also been seen to improve postreceptor insulin signaling and enhancing GLUT-4 translocation to the cell membrane [11]. Approximately 35% of the patients with diabetes go on to develop diabetic nephropathy [12]**.** The ACE inhibitor or ARB based treatments favorably affect the progression of diabetic nephropathy and reduce albuminuria [13]. ACE-inhibitors remove the tonic constrictor effect of angiotensin 2 on the efferent arteriole, lowering the glomerular intracapillary pressure while preserving renal plasma flow. They also interfere with the trophic properties of angiotensin 2 to promote cellular and glomerular hypertrophy and diminish the accumulation of mesangial matrix [14] preventing glomerular scarring. Taking into

consideration the guidelines and the clinical evidence in support of their use, utilization of the ACE-I/AT2RB class of drugs is low in the study. The guidelines underline the importance of this class of drugs by indicating that they should be used in all hypertensive patients who are diabetic. However they haven't been used in even half of the patients. Despite overwhelming evidence of their beneficial role in nephropathy, use further declines in this group of patients.

Diuretics help in reducing cardiovascular events and renal disease progression when combined with the ACE-I. Loop diuretics are effective in renal insufficiency, which justifies their high use in the group of patients suffering from nephropathy. Potassium sparing diuretics have been mostly avoided in these patients.

Addition of a calcium channel blocker to the ACE inhibitors or diuretics can help to achieve the target blood pressure [15]. Apart from their role in the control of blood pressure, renoprotection and attenuation in the decline of renal function in patients having nephropathy has also been shown by the use of the calcium channel antagonists [16]. Calcium channel blockers effectively reduce systemic blood pressure while maintaining the glomerular filtration rate and effective renal plasma flow [17]. Findings of pharmacokinetic studies suggest that there may be no need to modify the dosing of Amlodipine when prescribed for patients with nephropathy [18]. The particularly high utilization of the calcium channel blockers in this study can be attributed to achieving an optimal control of the blood pressure apart from the renoprotection afforded by it. The preference for Amlodipine in diabetics with and without nephropathy seems to relate to the positive pharmacokinetic findings which translate into convenient dosing in renal insufficiency.

To conclude, the JNC, very elaborately lays down guidelines for the drug management of diabetes with and without nephropathy, which to an extent, is reflected in the present study. Despite the abundant clinical evidence in support of the use of the ACE-I/AT2RB's in this particular subset of patients, their use does seem to be suboptimal. Optimal use of the angiotensin converting enzyme inhibitors along with the calcium channel blockers would definitely contribute to a better management of hypertension with diabetes. Further studies, at other tertiary centres, in this subgroup of patients would help to understand trends at a larger level, and give a better perspective to these findings.

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