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Use of Antihypertensives in Patients Having Associated Renal Parenchymal Disorders: Cross Sectional Prescription Pattern Study in a Tertiary Care Hospital

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ABSTRACT
Hypertension is both a cause and a consequence of renal parenchymal disease. Once detected, formulation of an appropriate therapeutic strategy is imperative to not only control hypertension, but also to retard the progression of the renal pathology. Judicious and optimal use of the available antihypertensive agents is of utmost importance. This study aims at analyzing the influence of current guidelines on prescribing in this particular subset of patients. Case history of patients having hypertension comorbid with renal pathological disorders was noted down from the medical records department. A total of 58 prescriptions thus noted were analysed on the basis of antihypertensive agents that were prescribed. The CCB's were the group of drugs prescribed the most in renal disease associated hypertension (79%) followed by the diuretics (48%).The ACE-inhibitors and ARB's were prescribed in around 34% of the patients. Amlodipine and Frusemide were the most frequently used individual agents.

Keywords: Antihypertensives, Prescription pattern, Renal parenchymal disease, Joint National Committee Guidelines, Pharmacoepidemiological study.

INTRODUCTION

Long standing, uncontrolled hypertension is linked to a plethora of systemic effects, prominent of which are its effects on the kidney. [1] Malignant or accelerated hypertension, renal artery stenosis and athero-embolic disease are all important causes of renal disease secondary to hypertension. More importantly, hypertension can ensue as a consequence of renal disease. Primary renal parenchymal disease has been observed to be responsible for 3%-4% of hypertension in some populations, and renovascular disease in around 1%. [2] Most patients (80-90%) presenting to renal replacement programmes are hypertensive. Diabetic nephropathy, hypertensive nephropathy and primary glomerulonephritis are the three most common causes of end stage renal failure worldwide. Other important aetiological factors include reflux nephropathy, polycystic kidney disease, analgesic nephropathy and secondary glomerulonephritis. Irrespective of whether hypertension causes renal disease or vice versa, it is clear that hypertension is a major determinant of progression of renal disease and the risk of end-stage failure. [3] There is also evidence that any familial tendency to hypertension will increase the prevalence of renal failure in patients with primary renal disorders [4] or with diabetes. [5] Clinical studies have shown that blood pressure control slows the disease progression in renal failure. [6] This underlines the importance of taking appropriate therapeutic measures so as to control hypertension as well as reduce the pathophysiological process associated with renal disorders.

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. The Sixth report of the JNC [7], as well as the seventh [8] documents major progress in the scientific basis for treatment of hypertension and recognizes advances in the availability of major new classes of drugs that have clear benefits in treating hypertension under certain conditions. The Indian guidelines, endorsed by the Cardiology Society of India, The Hypertension Society of India and the Indian College of Physicians closely follow the Joint National Committee Guidelines.

This study is an attempt to analyze the treatment of hypertension with associated renal parenchymal disease in a tertiary care hospital in perspective of the JNC Guidelines. Salient features related to the pharmacological basis and rationale of major classes of drugs in these patients has been briefly reviewed.

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MATERIALS AND METHODS

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 medicine OPD and Kasturba hospital Pharmacy. Patients coming to the medicine OPD as well as prescriptions that were being brought at the pharmacy were screened over a four month period (March 2004-July 2004). At the medicine OPD, only hypertensive patients receiving antihypertensive medication were included in the study. Amongst all the prescriptions that were screened at the hospital pharmacy, 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. Renal parenchymal disease was defined as a disorder pertaining to the kidney that was most likely to be the cause of hypertension in the patient and/or would pre-determine the choice of selection of an appropriate antihypertensive agent most suitable in the given clinical scenario. Biochemical, pathological and other clinical investigations obtained from the medical records of the patients enabled an aetiological classification of the renal disease. All the patients who were included in the study had serum creatinine levels beyond the normal range, indicating some form of renal impairment. Hypertension in children and adolescents included in the study was defined as systolic and diastolic blood pressure that was 95th percentile for gender, age and height. Only those patients having hypertension as the primary disease and renal parenchymal disease (as indicated by the pathological and biochemical investigations) as the secondary comorbid condition were included in the study. Patients not having hypertension despite having some form of renal disorder were excluded from the study. A total of 58 prescriptions thus obtained were included in the study. The different groups of antihypertensives prescribed in this selected group of patients were noted and the results thus obtained were analyzed.

RESULTS

The causes associated with renal parenchymal disease are shown in Table 1. The most commonly seen renal pathology is diabetes related nephropathy (35%). Mesangioproliferative glomerulonephritis (10%), nephrotic syndrome (8.6%) and polycystic kidney disease (5.2%) are the other important renal pathology seen in these patients. Around 60% of the patients were suffering from renal failure, many of whom had one or more underlying renal pathology.

Table 2 shows the overall use of antihypertensives in renal parenchymal disease. The calcium channel blockers have been used most extensively (79%). Amlodipine is the CCB used the most (72%) followed by Diltiazem (17%). The diuretics have been prescribed the most following the CCB's. Amongst the diuretics, Frusemide (75%) and the Thiazides (14%) have been the most commonly used. Potassium sparing diuretics like Spironolactone have been used sparingly. Utilization of the ACE-Inhibitors/AT2RB's is around 34%. Enalapril (45%) and Ramipril (40%) are the drugs from this group that have been mostly used.

Table 1: Pathological causes of renal parenchymal disease in the study population

Renal pathology	Number	Percentage
Diabetes related nephropathy	20	34.5
Mesangioproliferative glomerulonephritis	06	10.3
Nephrotic syndrome	05	8.6
Poycystic kidney disease	03	5.2
Pyelonephritis	03	5.2
IgA nephropathy	02	3.4
Renal transplant	02	3.4
Renal artery stenosis	01	1.7
Hydronephrosis	01	1.7
Polyarteritis nodosa	01	1.7
Renal failure	35	60.3

Table 2: Antihypertensive drugs used in the study population having renal parenchymal disease along with hypertension

Antihypertensive drug class	Drug	Renal parenchymal disease Total-58	Percentage
Calcium channel blockers	Amlodipine	33	
	Diltiazem	08	
	Nifedipine	04	
	Felodipine	01	
		Total : 46	**79.3**
Beta blockers	Atenolol	10	
	Carvedilol	06	
	Metoprolol	01	
	Propranolol	01	
	Nebivolol	01	
		Total : 19	**2.7**
ACE-I/AT2RB	Ramipril	08	
	Enalapril	09	
	Fosinopril	01	
	Losartan	02	
		Total: 20	**34.4**
Diuretics	Frusemide	21	
	Thiazides	04	
	Spironolactone	03	
		Total: 28	**48.2**
Miscellaneous drugs	Clonidine	14	
	Prazocin	04	
	Doxazosin	01	
		Total: 19	**32.7**

Table 3: Comparative status of monotherapy and combination therapy prescriptions in the study population

Relative use of monotherapy & Combination therapy	Prescriptions of renal parenchymal disease Total-58	Percentage
Monotherapy	17	29.3
Calcium channel blockers	08	47
Beta blockers	01	5.9
ACE-I /AT2RB	07	41.2
Clonidine	01	5.9
Combination therapy	**41**	**70.6**
Two -drug combination	20	48.8
Three- drug combination	14	34.1
Four/more- drug combination	07	17

Table 3 shows the relative use of monotherapy and combination therapy. Combination therapy comprising two, three or more drugs have been used more frequently (71%) than monotherapy (29%). The calcium channel blockers (47%) and the ACE-Inhibitors/AT2RB's (41%) are the group of drugs used most frequently as monotherapy. The diuretics have always been used only in combination with other agents. A two drug combination has been used most

frequently (49%), followed by a three drug combination (34%).

Table 4 and 5 show the relative use of antihypertensives in both genders and two age groups.

Table 4: Relative use of antihypertensive drug groups in males and females of study population

Drug Class	Males Total-39	Percentage Total-67.2	Females Total-19	Percentage Total-32.8
CCB's	34	87.1	12	63.2
Beta-blockers	13	33.3	06	31.6
ACE-I/AT2RB	08	20.5	08	42.1
Diuretics	20	51.3	08	42.1
Clonidine	09	23.0	05	26.3
Prazocin/ Doxazosin	04	10.2	01	5.3

Table 5: Relative use of antihypertensives in two age groups of the study population

Drug class	<55Yrs Total- 40	Percentage 69	>55Yrs Total- 18	Percentage 31
CCB's	31	77.0	15	83.3
Beta-blockers	12	30	07	38.9
ACE-I/AT2RB	16	40	04	22.2
Diuretics	15	37.5	13	72.2
Clonidine	09	22.5	05	27.7
Prazocin/ Doxazosin	03	07.5	02	11.1

DISCUSSION

Renal parenchymal hypertension represents an interaction of many independent mechanisms. Potential factors include sodium retention leading to volume expansion, increased pressor activity and decrease in endogenous vasodepressor compounds. [9] Treatment of hypertension has been shown to retard the rate of progression of renal impairment in several disease states. In patients having diabetic or non-diabetic renal disease, vital factors for preserving residual renal function include adequate control of blood pressure and blockade of the renin-angiotensin pathway. The major mode of action of certain antihypertensive groups, like the ACE-Inhibitors and the angiotensin receptor blockers (AT2RB's), is by virtue of their effects on the renin-angiotensin pathway. As far as hypertension is concerned, all classes of antihypertensive drugs are effective in reducing the blood pressure. Optimal control of the blood pressure may however require the combined use of multiple antihypertensive agents. Each one of the groups of antihypertensives has distinct features in terms of pharmacological actions and mode of action. Salient features of antihypertensive groups that are vital in the treatment of hypertension related to renal parenchymal disorders are mentioned below. These include the loop and thiazide diuretics, ACE-Inhibitors/AT2RB's and the calcium channel blockers.

The loop diuretics are the agents of choice for the management of extracellular fluid volume expansion and hypertension when the glomerular filtration rate falls below 30 ml/min. [10-12] Unlike the thiazide diuretics, the loop agents are effective natriutetic agents at glomerular filtration rates well below 30ml/min, even when used alone, although very high doses may be required as renal failure progresses. Thiazides alone are not usually effective natriuretic agents in a patient with a serum creatinine concentration above 2.0 mg /dl or a creatinine clearance below 30 ml/min [11], probably because of diminished delivery of the sodium load to the distal nephron and of the drug to its site of action. Therefore, the use of Thiazides alone is not recommended at low levels of renal function. A minority of hypertensive patients with chronic renal failure are "volume unresponsive". [13-14] These patients are characterized by hypertension refractory to sodium restriction and diuretics and often require the addition of potent non diuretic antihypertensive agents, such as the calcium channel blockers and the ACE inhibitors/AT2RB's. ACE inhibitors decrease blood pressure and urinary protein excretion, slow the increase in serum creatinine and reduce the incidence of end stage renal disease (ESRD).The beneficial effect of ACE inhibitors is stronger in patients with greater proteinuria at the onset of therapy. [15] Administration of ACE inhibitors decreases glomerular capillary pressure, with a resultant reduction of glomerular sclerosis, suggesting that ACE inhibitors may protect the kidney from hemodynamically mediated glomerular damage. [16]

Calcium channel blockers are effective antihypertensive agents for treating patients with chronic renal impairment. Findings of pharmacokinetic studies suggest that there may be no need to modify the dosing of Amlodipine, when prescribed for patients with renal failure. [17] A comprehensive review on calcium antagonists and chronic renal failure concluded that, both in patients with essential hypertension and in patients with chronic renal insufficiency, calcium antagonists effectively reduce systemic blood pressure while maintaining the glomerular filtration rate and effective renal plasma flow. [18] Results from a few long term studies suggest that calcium antagonists may attenuate the decline in renal function of patients with chronic renal failure.

In view of these findings, guidelines suggest that most patients having renal parenchymal disorders should receive an ACE inhibitor (in most cases in combination with a diuretic) to control hypertension and to slow progressive renal failure. [19-21] Thiazide diuretics are not effective with advanced renal insufficiency (serum creatinine level > 2.5 mg/dl), and loop diuretics are needed. Combining a loop diuretic with a long acting thiazide diuretic such as metolazone is effective in patients resistant to a loop diuretic alone. Potassium sparing diuretics should be avoided in patients with renal insufficiency.

The high utilization of the calcium channel blockers seen in this study, probably reflects the safety profile that they have in renal parenchymal disorders, apart from their ability to reduce blood pressure. It is not surprising that Amlodipine is the most frequently used individual drug amongst all the antihypertensive groups, considering its pharmacokinetic properties in renal disorders. The diuretics, Frusemide in particular, have also been used frequently, underlining their utility in renal disorders associated with low filtration rates. These agents have however, not been used alone, as they are not suitable drugs for the control of hypertension. Utilization of the agents that act by inhibiting the renin angiotensin pathway- the ACE-Inhibitors and the AT2RB's, seems to be low, considering the paramount beneficial effects they show in retarding the pathology of renal parenchymal disorders. The large number of patients suffering from renal failure could be a possible deterrent in prescribing these agents more frequently. There is a clear emphasis on the use of combination therapy over monotherapy. This again is probably in order to achieve an optimal control of hypertension, which otherwise, would not be possible with the use of a single agent. Gender and age do not seem to have

a bearing on the selection of a particular antihypertensive agent in renal parenchymal disorders.

To conclude, renal parenchymal diseases aetiologically include a heterogenous group of pathological disorders. The underlying renal pathology may require specific therapeutic intervention. The Joint National Committee Guidelines considers hypertension due to renal pathology as a homogenous group. In this study, the use of antihypertensives in this particular group of patients does not deviate from the guidelines laid down by the Joint National Committee. Further large scale studies carried out at other tertiary care centres would help to compare, analyze and rationalize prescribing trends in renal parenchymal hypertension, giving a broader perspective to these findings

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