Original Article

Pharmacology Section

Compliance and Adverse drug Effects of Antihypertensives in Rural India

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ABSTRACT

Background: Hypertension is the most prevalent health problem among adult primary care patients, but its recognition and treatment are suboptimal. Adherence and persistence have been studied in patients of hypertension in this study.

Material and Methods: 491 patients suffering from hypertension and coming to the OPD of a rural medical hospital in Loni were examined in a prospective study over a year after giving the prescribed antihypertensive medication from Oct 2004 to May 2006.

Results: A decrease in blood pressure was observed in patients treated with one pill per day as compared to patients being treated with two and three pills per day. Compliance was significantly better in patients in combination therapy as compared to monotherapy. Cost is an important determinant in deciding compliance.

Conclusion: Low dose combination therapy is more effective and is well tolerated than high dose monotherapy. Moreover, the incidence of ADR was observed to be significantly lower with low dose combination therapy in addition to better compliance.

Key Words: Compliance, Antihypertensives, Rural

INTRODUCTION

Hypertension is a common cardiovascular disorder, which is an important risk factor for coronary artery disease. Though many drugs are available for the treatment, it still remains poorly controlled in both industrialized and even more prevalent in developing countries [1, 2]. Poor compliance to the prescribed drugs poses a major problem among patients with hypertension, heart disease, depression and others. A special case of non compliance is the primary non compliance, patients not redeeming their prescriptions [3]. It is a well known fact that frequency of doses play an important part, single dose has been found to improve compliance but 24 hour antihypertensive activity should be provided by the drug [4-6].

Patient's non compliance with the therapeutic regimen has long been a challenge for practitioners, hence this study has been undertaken to investigate the adherence and persistence of antihypertensive drugs in Indian rural population as well as monitoring adverse drug reactions and its relation to compliance.

MATERIAL AND METHODS

The study model included 491 patients visiting the OPD of rural medical hospital in Loni who were diagnosed with stage I and II hypertension from Ist Oct 2004 to Ist may 2006 [Table/Fig-1]. Ambulatory patients aged 30 to 60 years with newly diagnosed stage (SBP 140-159 and DBP 100-109 mmhg) and stage II (SBP 160-179, DBP 100-109 mmhg) hypertension, as defined by the sixth report of the joint committee on prevention, detection, evaluation and treatment of high blood pressure were included. However, patients with stage III or secondary hypertension or a history of myocardial infarction, cardiac intervention or stroke, pregnant or breast-feeding women and patients with cardiac, hepatic, renal neurological, metabolic or any other systemic disorder were excluded from the study. Also patients with raised transaminases,serum creatinine and patients hemoglobin of less than 10 gm/dl were also excluded from the study.

Patients fulfilling the inclusion and exclusion criteria were enrolled and treated for hypertension in a follow up of one year, with evaluation of their demographic profile and medical history by self prepared questionnaires, and assessment of vital signs at each visit every month, while laboratory tests were conducted at the beginning and end of study. Treatment was initiated with one or a low dose combination of atenolol, enalpril, losartan, amlodipine or hydrochlorothiazide and patients were monitored for adverse drug events. During follow up patient's BP was measured as an average with readings taken at 10 minutes interval with a standard mercury sphygmomanometer. Patients were made to complete a medication compliance card and were assessed according to a pro-forma.

The level of compliance was determined by the medical compliance card at the end of study and a patient was considered compliant with the study medication if at least 86 percent of the study medications had been applied/consumed according to prescribed regimen. The compliance was considered satisfactory when the mean compliance was more than or equal to 86 percent, which corresponded to taking medication for six or seven days per week on an average [7]. Adverse reactions were divided into mild, moderate, or severe and assessed for date of onset, duration and action taken regarding study drug. Statistical evaluations were made using t-test and Z test to obtain relevant p values.

RESULTS

The study cohort included 293 men (mean age, $\pm$ SD 45.6 $\pm$ 9.8 years), and 198 women (47.6 $\pm$ 8 years) [Table/Fig-1]. Of the 208 participants taking one pill everyday, 76 were regular attendees while 132 were irregular attendees to the follow up visits and were associated with a mean satisfactory compliance of 58 percent and 6.2 percent respectively. The mean satisfactory compliance was 39 percent and 4.9 percent in 23 and 52 participants who took two pills a day, respectively. The study group taking three pills a

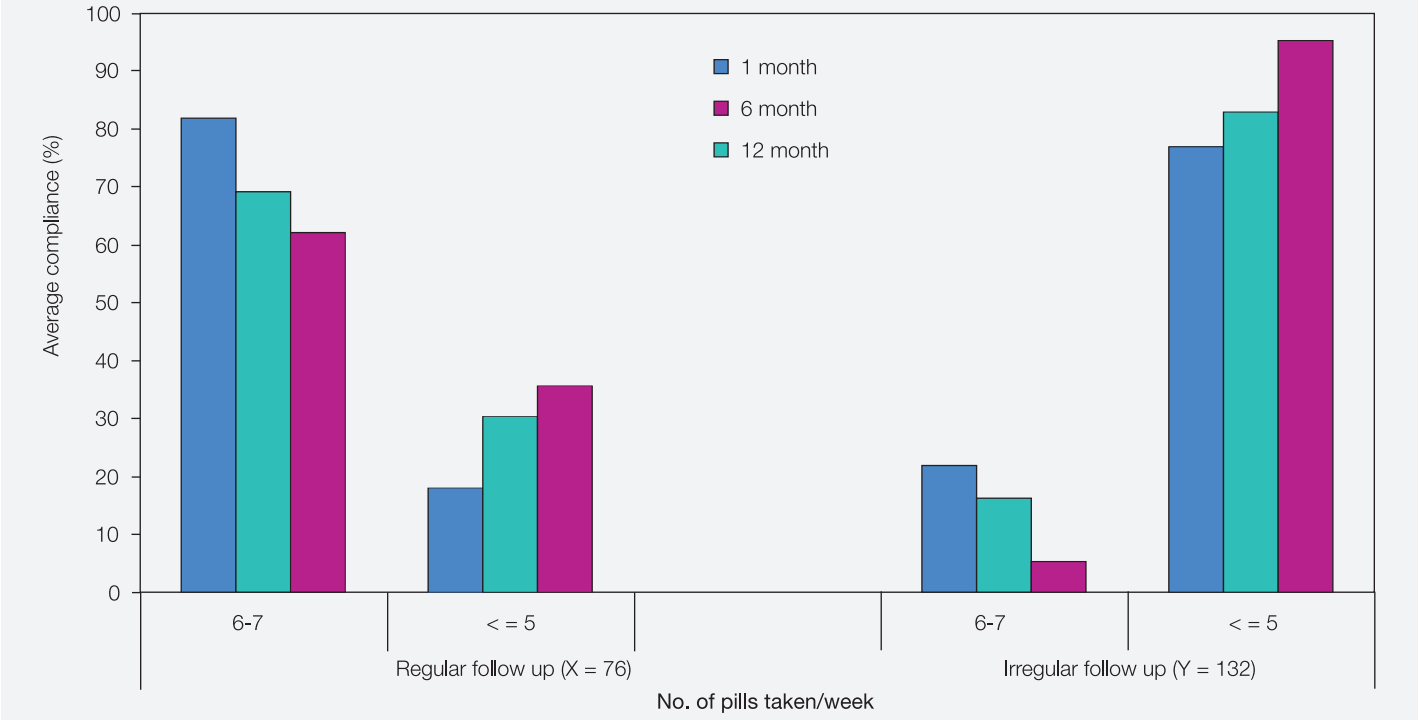
Parameters		
Age (yrs)	Male	45.6 ± 9.8 years
	Female	47.6 ± 8 years
Weight (kg)	Mean	67.47 ± 11.45
	Range	40-98 kg
Height (cm)	Mean	158.95 ± 7.42
	Range	136-178 cm
Sex (%)	Male	293 (59.7%)
	Female	198 (40.3%)
	Total Participants	491

[Table/Fig-1]: Demography of participants

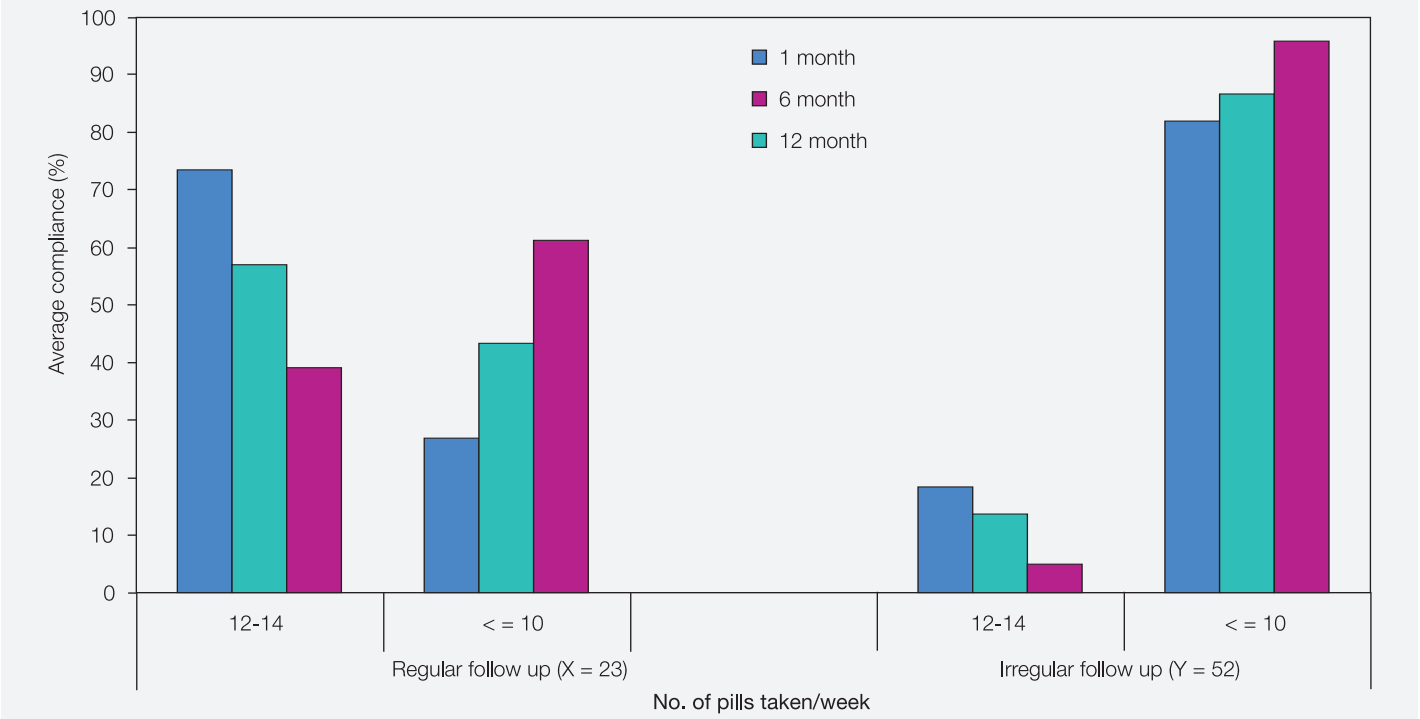
day were associated with a mean satisfactory compliance of 28.3 percent and 3.7 percent in 12 regular and 25 irregular patients, respectively [Table/Fig-2], [Table/Fig-3], [Table/Fig-4].

The mean blood pressure in the initial 491 patiens was 159 ± 14/100 ± 09 mmHg. The fall in blood pressure was insignificant for patients who dropped out of treatment (p>0.005).

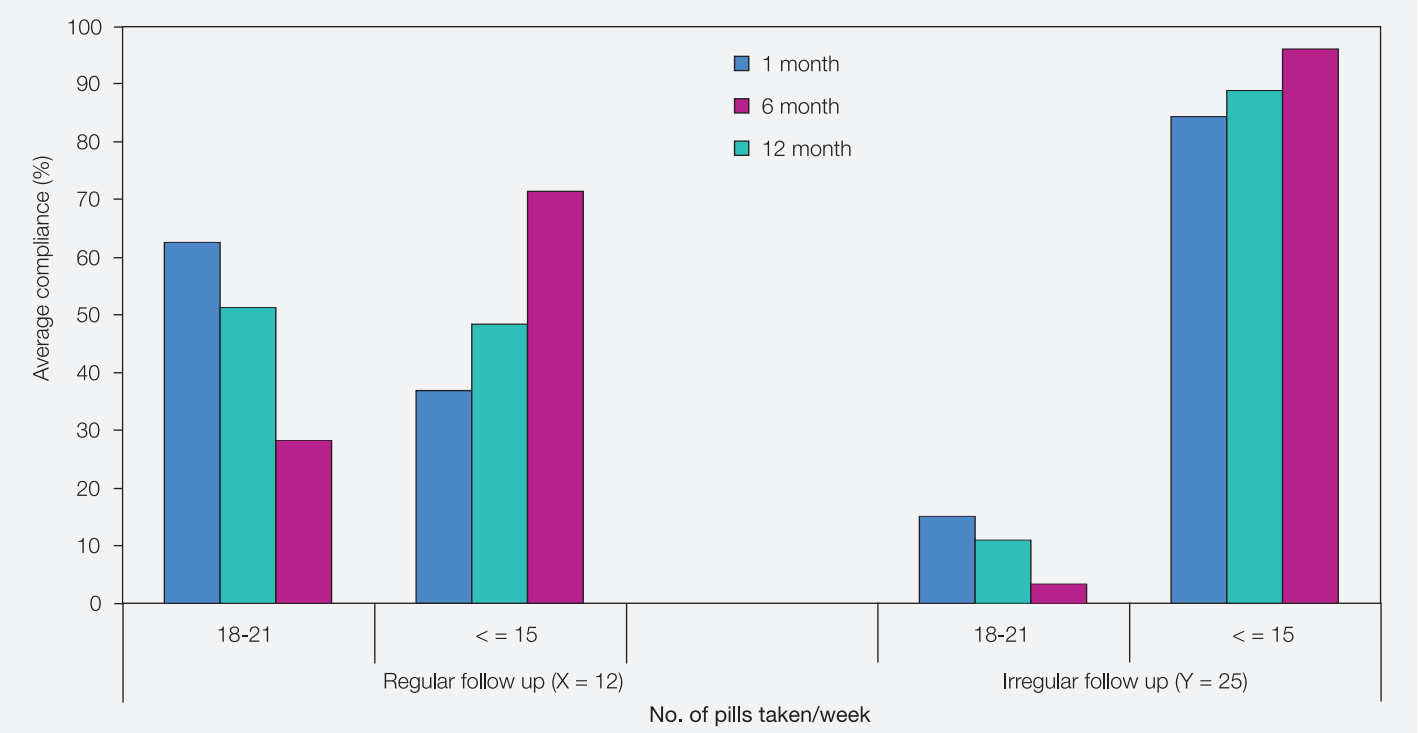
Mean blood pressure at the end of treatment at one year was 149 ±11/96 ± 8 mmHg for the continuing patients, whereas the mean difference in blood pressure before treatment and at 12 months of treatment was 17 ± 11/11± 6 mmHg for participants taking medication 6-7 days per week, 11 ± 6/8 ± 7 for those taking medication 4 to 5 days a week and 5 ± 8/5 ± 4 for those taking



[Table/Fig-2]: Average compliance to one pill day antihypertensive medication by month of medical followup and category of adherence to followup



[Table/Fig-3]: Average compliance to two pills day antihypertensive medication by month of medical followup and category of adherence to followup



[Table/Fig-4]: Average compliance to three pills day antihypertensive medication by month of medical followup and category of adherence to followup

No of tablets per day	Drugs	Cost			No. of patients taking medication
		Per table	Per day	Per/30 day	
One	Tab. Hydrochlorothiazide 12.5 mg + Enalapril 10 mg	3.55	3.55	106.50	63
	Tab. Losartan 25 mg + Hydrochlorothiazide 12.5 mg	5.40	5.40	162.00	40
	Tab. Enalapril 10 mg	3.10	3.10	93.00	28
	Tab. Atenolol 50 mg	2.20	2.20	66.00	16
	Tab. Atenolol 50 mg + Tab. Hydrochlorothiazide 12.5 mg	2.15	2.15	64.50	12
	Tab. Losartan 50 mg	5.58	5.58	167.40	15
	Tab. Amlodipine 5 mg + Atenolol 25 mg	3.41	3.41	102.30	38
Two	1) Tab. Atenolol 25 mg 2) Tab. Hydrochlorothiazide 12.5 mg + Enalapril 10 mg	1.54 3.55	5.09	152.0	42
	1) Tab. Losartan 25 mg + Hydrochlorothiazide 12.5 2) Tab. Atenolol 25 mg	5.40 1.54	6.94	20.20	37
Three	1) Tab. Atenolol 50 mg 2) Hydrochlorothiazide 12.5 3) Tab. Losartan 50 mg	2.19 0.67 5.58	8.44	253.20	17
	1) Tab. Enalapril 10 mg 2) Tab. Atenolol 50 mg 3) Hydrochlorothiazide 12.5	3.10 2.19 0.67	5.96	178.80	14
	1) Tab. Atenolol 25 mg 2) Tab. Amlodipine 10 mg 3) Hydrochlorothiazide 12.5	1.54 2.49 0.67	4.70	141.00	6

[Table/Fig-5]: Expenses on drugs per day and per month & number of participants taking medications

medication for zero to three days a week. Differences between highest and lowest compliance categories were significant both for systolic and diastolic blood pressure measurements ($p < 0.005$).

Optimal blood pressure control was only achieved in 8.6 percent participants which is consistent with many Indian studies [8-10].

Cost of therapy adversely and inversely affected the compliance to treatment [Table/Fig-5]. Many adverse drug reactions were observed which included dry cough (n=10), which subsided in all patients except two who had to be shifted to losartan therapy, weakness (n=13), headache (n=4), mild dizziness (n=11), dryness of mouth (n=12) and one patient with ankle swelling [Table/Fig-6]. Low incidence of adverse drug reactions could be attributed to the use of low dose combinations instead of high dose monotherapy.

DISCUSSION

The results of this study showed that only 58 percent of the participants taking one pill a day and visiting regularly maintained satisfactory compliance to medication over a period of 12 months. The lowest level of compliance was associated with patients taking three pills a day with 28.3 percent in patients visiting regularly and 3.7 percent in those visiting irregularly which suggested that number of pills is directly proportional to compliance level. Percentage of drop outs from the therapy also increased with the increase in the

Event	Medication possible for ADR	Incident of ADR								
		One pill/day			Two pills/day			Three pills/day		
		X	Y	Total	X	Y	Total	X	Y	Total
Dry cough	Enalapril, Losartan	4	1	5	3	0	3	1	1	2
Weakness	Atenolol, Thiazide	3	1	4	3	2	5	3	1	4
Headache	Amlodipine, Thiazide	2	1	3	1	0	0	1	0	1
Dizziness	Enalapril, Losartan, Amlodipine, Thiazide	4	2	6	2	0	2	2	1	3
Frequency of urination	Thiazide	5	2	7	2	1	3	2	0	2
Dryness of mouth	Atenolol	4	1	5	3	1	4	2	1	3
Ankle swelling	Amlodipine	1	0	1	0	0	0	0	0	0
Gastric irritation	Amlodipine & Others	2	0	2	4	2	6	2	1	3

[Table/Fig-6]: Adverse drugreactionprofile of patients during study period
X = Percentage of participants who attended medical visits regularly (did not miss any visits)
Y = Percentage of participants who attended medical visits irregularly (missed more than one visit)
One pill/day (X = 76 & Y = 132)
Two pills/day (X = 23 & Y = 52)
Three pills/day (X = 12 & Y = 25)

number of pills per day, with 32 percent for patients taking one pill per day to 45.6 percent for patients taking three pills per day. A total of 171 patients dropped out during the therapy.

A decrease in compliance was seen over time, particularly in the first three months which could be attributed to decrease in motivation since it's a silence or its association with real or imaginary discomfort.

Combination therapy is advantageous as compared to mono-therapy, which is shown in the higher response ratio for the former [11-12]. Review of literature emphasis on the fact that compliance is better in patients taking simpler form of medication regimes than the complicated ones [13-17].

Blood pressure was found optimally reduced in 8.6 percent in the study, while the NHANES III survey found that optimal blood pressure control was only 23 percent in the American population [10]. Satisfactory results for compliance were associated with a greater decrease in blood pressure as compared to poor compliance [18-19].

Many factors were found associated with low compliance which included male gender, young age, initial drug choice, education level, living alone, unemployment including others [20-22]. Education was tied to better compliance since they have a better understanding of the long term consequences [23-24]. Cost of the antihypertensive drug therapy was found to be inversely proportional to compliance [25-26]. Patients on multiple therapy were more likely to develop adverse drug reaction as compared to patients on monotherapy [27-28].

Dry cough was associated with enalpril and losartan while amlod-ipine and thiazide was associated with mild headache. Thiazide was also found associated with increased frequency of micturition in the patients. One patient on amlodipine therapy reported of ankle swelling. Mild severity of side effects could be attributed to low doses used in combination therapy.

CONCLUSION

Low dose combination therapy is more effective and is well tolerated than high dose monotherapy. Moreover, the incidence of ADR was observed to be significantly lower with low dose combination therapy in addition to better compliance. The low level of compliance to antihypertensive medication found in this study, is consistent with findings in other countries and studies in India, emphasizing the need of population wide primary prevention of elevated blood pressure and cardiovascular disease. Such measures include educational, legislative, and fiscal actions to encourage the adaptation of a healthy diet and to increase the facilities and opportunities for physical activity at leisure.

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