ORIGINAL RESEARCH PAPER

General Medicine

THERAPEUTIC RESPONSE AND ADVERSE EFFECTS WITH START – UP DOSE OF RAMIPRIL IN ESSENTIAL HYPERTENSION

KEY WORDS: ACE inhibitors, Hyperkalaemia, Dry Cough.

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ABSTRACT

Adult patients attending Medicine outpatient department, diagnosed as suffering from essential hypertension were enrolled (n=640) for comparative analysis of starting dose and ADE of Ramipril. The patients with mild HTN were prescribed Ramipril 2.5 mg single dose once a day and those with moderate HTN were prescribed Ramipril 5 mg once a day. These patients were followed weekly at Hypertension clinic for examination and investigations, Cumulative target BP achievement was found at 10th week for mild and 12th week for moderate hypertensive subjects. Dry cough incidence was almost equal in both HTN categories this finding suggest that cough as an ADE of ACEI is independent of type of HTN and dose of drug. Hyperkalaemia incidence appears to follow the grading of HTN and also shows the dose dependent response relationship, other renal function is not affected by Ramipril.

INTRODUCTION

Pharmacotherapy of essential hypertension (HTN) may continue lifelong[1], therefore, besides achieving the target of desired blood pressure (BP), it is equally important to curtail the adverse drug effects (ADE). Such approach may prevent the complications of disease and restrict ADE. Angiotensin converting enzyme inhibitors (ACEI) are the choice drug for hypertension. Lisinopril, ramipril are extensively prescribed ACEI. These are known to cause iatrogenic ADE such as hyperkalaemia; and cough[2, 3]. Hyperkalaemia may produce asymptomatic / undetectable complications of cardiac rhythm. Moreover the cardiac ADE in ambulant outpatient hypertensive population is hazardous and may prove catastrophically fatal[2,4]. It has been observed that physicians, cardiologist are prescribing variable doses of drug based on clinical scenario, which may be due to a wide range of dose mentioned in literature e.g. 1.25 – 20 mg/day with a step care approach[1], 5-10mg/day[5]. Therefore selection of a dose of drug becomes a complicated task.

Essential hypertension in later stages may lead to varieties of complications e.g. - vascular, renal, cerebral, coronary heart disease and others[5]. Since the therapy is prolonged, drug induced ADE must be controlled by prescribing minimum effective dose of drug in the beginning. Hypertension is graded as mild, moderate, severe[5]. There are no transparent guidelines about prescription of initial dose of ramipril for different grades of HTN with respect to desired response and minimal ADE.

AIM:

To assess the optimum dose of Ramipril as mono-therapy in mild and moderate hypertension and to explore the ADE.

METHODOLOGY

This study was cleared by Institutional ethical committee.

Adult Male patients attending Medicine outpatient department, diagnosed as suffering from essential hypertension were approached for the study. A written, informed, signed consent was obtained and then they were screened for clinical examination, ECG and haemo-biochemical investigations.

Inclusion criterias

1. BP (mmHg).
(a) mild HTN = 140-159/90-99,
(b) moderate HTN = 160-164/100-104[5]
2. Nil significant systemic examination findings.
3. CBC, urine exam, Blood sugar, serum electrolyte (Na^+, K^+), Serum creatinine, blood urea, thyroid and lipid profile, ECG within normal range.
4. No history of allergy, Bronchial asthma, No Family H/O diabetes mellitus, ischaemic heart disease/ sudden death, stroke.

Exclusion criterias

1. Patients who needed indoor management.
2. Poly-diagnosis.
3. Abnormal ECG and baseline investigation reports.
4. Patients taking other drug affecting S. electrolyte viz. beta blockers, NSAID, K^+ sparing diuretics, consuming high K^+ containing fruits/diet.
5. Evidence of renal insufficiency, diabetes mellitus.
6. Patients with Renal Arterial Stenosis.

The patients with mild HTN were prescribed Ramipril 2.5 mg single dose once a day (OD) and those with moderate HTN were prescribed Ramipril 5 mg once a day. These patients were followed weekly at Hypertension clinic for examination and investigations[5], the reports were obtained online, noted in master excel sheet on computer. The target BP aim was fixed at 135-140/80-85 mmHg[3].

RESULT

The distribution of Age and HTN of patients enrolled in the study is shown in Table- 1.

Table- 1: Age wise distribution of patients with mild and moderate Hypertension

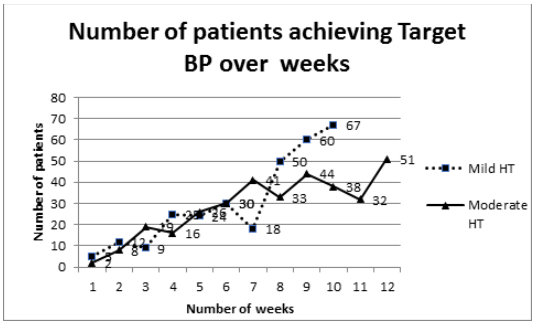
Age in years	Blood pressure grade		Total
	Mild HTN	Moderate HTN	
31-40	55	60	115 (18%)
41-50	83	110	193 (30%)
51-60	162	170	332 (52%)
Total	300 (47%)	340 (53%)	640

The figure shows that out of 640 patients there were 300 patients of mild hypertension i.e. 47% and 340 patients (53%) are of moderate hypertension. More than half (52%) patients are above 50 years of age.

Weekly follow up for clinical examination, investigations were

done; Number of patients who achieved target BP (135-140/80-85 mmHg) at different week intervals is as shown in Figure- 1.

Figure- 1: Weekly record of number of patients achieving target BP.



The number of patients having achieved target BP at the end of one week is five (5/300) for mild and two (2/340) for moderate HT, cumulative maximum response (Cmax) was observed at week 10 for mild HTN i.e. (67/300) and, week 12 for moderate HTN i.e. (51/340).

Adverse drug effects were carefully watched; There was complaint of dry cough and the blood investigation reports revealed hyperkalaemia as shown in Table- 2.

Table- 2: Number of patients showing Adverse drug effects with Ramipril

Week	Adverse effects			
	Mild HTN		Moderate HTN	
	Cough	K+*	Cough	K+*
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	2	0	0	0
6	1	0	1	1
7	2	0	0	0
8	1	0	1	1
9	0	0	2	1
10	0	0	3	0
11	1	0	1	1
12	4	1	3	2
Total	11	1	12	5
(Percent)	(3.6%)	(0.30%)	(3.50%)	(1.40%)

K^+ = Hyperkalaemia (K+> 5.5 mEq/dl)[7].

Table- 2 shows the incidence of ADE in mild and moderate HTN observed over 12-week period. Dry cough was seen in 11 (3.6%) in mild and 12 (3.5%) in moderate HTN. Hyperkalaemia was observed in 1 patient (0.3%) with mild HTN and 5 patients (1.4%) with moderate HTN.

Serum creatinine and blood urea reports were found within physiological range.

DISCUSSION

Ramipril is recommended in management of HTN as a first step in the in 4 step-care approach model[5]. The ADE of ramipril such as hyperkalaemia warrants cautious prescribing, as this may prove detrimental for cardiac function, more so in ambulatory patients.

The present study was planned to assess the optimum dose for initiation of ramipril in mild and moderate HTN and study the ADE over a period of 12 weeks, six hundred and forty patients of mild and moderate HTN were enrolled in the study, and were categorised in three age groups of 31-40, 41-50 and 51-60.

More than 50% of patients showed moderate HT. There were more number of patients above 50 years in both the groups suggesting that advancing age is more prone to HTN which corroborates well with the literature information[3].

The first follow up at one week has shown 5 and 2 responders who achieved target BP value of mild and moderate HTN category. It is possible that the actual target may have been achieved earlier somewhere during one week period. Cumulative target BP achievement was found at 10th week for mild and 12th week for moderate hypertensive subjects; ACE inhibitory action of ramipril the desired response appear early for mild HTN category, despite lower dose (2.5 mg). Therefore it could be surmised from this study that the disease response follows direct proportionate relationship, which corroborates well with the concept of dose-response dynamics[6]. Further increase in dose may yield still early response in a greater number of patients. However such approach may result in increase in adverse effects which can otherwise be avoided. Since inhibition of any biogenic amine /enzyme etc. means interfering with other physiological function.It is interesting to note that maximum number of patients responded at week10 and week12 for both HTN patient groups, which may indicate that gradual and thus cumulative ACE inhibition is at its peak as the time passes. It may be advisable to adopt wait and watch policy in achieving therapeutic target in some cases; compromising the delay in target response. Intermittent variability in number of responders may be due to biological variation or fluctuation of ACE inhibition profile. Hence the initial dose of ramipril appears justified in present set-up.

Dry cough incidence was almost equal in both HTN categories (3.6%, 3.5%), this finding suggest that cough as an ADE of ACEI is independent of type of HTN and dose of drug. The mechanism of dry cough is described due to parallel and mere inhibition of metabolism of substance P and bradykinin besides ACE inhibition. However when relevant investigations were carried out related to cough, no cause was detected. Hyperkalaemia[3] (serum potassium >5.5 mEq/L) was observed in 1 (0.3%; K+ 5.6 mEq/L) and 5 (1.4%; K+ 5.6—5.8mEq/L) subjects of mild and moderate HTN category respectively. Though symptom free, these patients were at risk of related complications; weekly follow-up could make it possible to initiate appropriate treatment. The hyperkalaemia was documented in mild HTN (ramipril 2.5mg) at week 12, and in moderate HTN (ramipril 5mg) a little early i.e. at week 8 follow up. Hyperkalaemia incidence appears to follow the grading of HTN and also shows the dose dependent response relationship dynamics[6]. The mechanism is known as due to interference of renin-angiotensin adrenal axis causing ACE inhibition, thus leading to inadequate excretion of K^+. It is reported that ACEI also block the adrenal gland response to hyperkalaemia, in turn attenuating direct stimulation of aldosterone release which could otherwise occur in presence of increased potassium concentration[7]. In addition we assume that grading of HTN may have influence on renin-angiotensin-adrenal axis for serum potassium conservation, based on finding that moderate hypertensive developed this ADR in more number of patients and at early biological lag[8]. In moderate HTN, the ACE inhibition required may be more for target response to be achieved. Serum creatinine, blood urea and other electrolyte values were normal throughout the study in all sample population, so we believe that renal function is not affected by ramipril.

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CONCLUSION

ACEI are recommended as monotherapy in mild and moderate hypertension. Prevalence was more in age group 51-60 yr. (52%); moderate HTN was more among all patients(53%). Cumulative target of 140/80-85 mmHg as 100% response was observed at week 10 in mild and week 12 in moderate HTN respectively.

Adverse drug effects in both HTN categories were observed as dry cough (3.6%; 3.5%) and hyperkalaemia (0.3%:1.4%), apparent insignificant difference of dry cough relates to parallel inhibition of metabolism of substance p and bradykinin; may be unrelated to propensity of ACE inhibition. Hyperkalaemia documented can be attributed to renin-angiotensin pathway inhibition with few other mechanisms. There was no change in other renal function test value, indicate that ramipril preserve renal function.

The result of our study focusses on evidence that ramipril in the start-up dose of 2.5 mg in mild and 5 mg in moderate essential hypertensive should be preferred, so as to avoid the catastrophical risk of undiagnosed, asymptomatic hyperkalaemia.

REFERENCES

1. Inhibitors of renin angiotensin system.In: Goodman and Gillman. The Pharmacological Basis of Therapeutics, Bruton, Chabner, Knollman(Ed), 2011;12:p 732.
2. Inhibitors of renin angiotensin system. In: Goodman and Gillman. The Pharmacological Basis of Therapeutics, Bruton, Chabner, Knollman(Ed), 2011;12:735-736.
3. Hypertensive vascular disease. In: Harrisons Principle and Practice of Internal Medicine. Lango, Fauci, Kasper, Hauser, Jameson, Loscalzo (Ed), Mac Graw hills, 2012;1;18:2056—2057.
4. Regulation of renal function and vascular volume. In: Goodman and Gillman. The Pharmacological Basis of Therapeutics, Bruton, Chabner, Knollman(Ed), 2011;12:671-700.
5. Hypertension. In:Davidson's principle and practice of Medicine, Walker, Colledge,Ratson,Penman (Ed). Churchill Livingstone,Elsevier, 2014;22:607-13.
6. Dose response relationship: InGoodman and Gillman.The Pharmacological Basis of Therapeutics, Bruton, Chabner,Knollman(Ed), 2011;12:p 36.
7. Hyperkalaemia In: Harrisons Principle and Practice of Internal Medicine. Lango, Fauci, Kasper, Hauser, Jameson, Loscalzo (Ed), Mac Graw hills, 2012;1;18:p 355.
8. Makoto Daimon, Aya Kamba, Hiroshi Murakami et al. Association between pituitary-adrenal axis dominance over the renin-angiotensin-aldosterone system and hypertension: J Clin Endocrinol Metab. 2015 : doi: 10.1210/jc.2015-3568.