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Research Article

EVALUATION OF AMLODIPINE BESYLATE IN THE TREATMENT OF ISOLATED SYSTOLIC HYPERTENSION IN INDIAN PATIENTS

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ABSTRACT

Aim: The aim of the study was to evaluate tolerability and benefits of Amlodipine besylate in adult Indians with Isolated Systolic Hypertension.

Methods: This was a phase IV, multicentric, open labeled, prospective study conducted in the outpatient setup. Eligible patients who gave written informed consent, were treated with Amlodipine besylate (2.5-10mg/day) and evaluated frequently till the treatment goals were achieved (SBP < 140 mm Hg).

Results: Of 1770 patients who received Amlodipine besylate, 93.88% achieved the desired therapeutic response. 24.01% of patients responded to the treatment within 14 days. There was a significant association between the grades of ISH and initial dose prescribed, with grade III patients requiring higher dose. There was an association between the previously untreated and inadequately treated groups and the initial dose of Amlodipine besylate (p=0.00), with higher dose being prescribed to the latter group. The drug was well tolerated.

Conclusion:Amlodipine besylate is an effective, well tolerated antihypertensive agent in adult Indian patients with isolated systolic hypertension and exhibits a good safety profile.

Keywords: ISH, Amlodipine besylate.

INTRODUCTION

Isolated Systolic Hypertension (ISH), a common subtype of hypertension, is a poorly diagnosed, under- treated condition and is a major risk factor for cardiovascular and total mortality.[1] Prevalence of ISH increases with advancing age; according to the National Health and Nutrition Examination Survey (NHANES III), ISH accounts for 54% of hypertension in patients aged 50 to 59 years and 87% in patients aged 60 years or older.[2] A study by AK Gupta et al has shown that prevalence of ISH in Shimla (INDIA) was 7.78%.[3] Prevalence rate of ISH in hypertensive women in five Indian cities was 50.5%.[4]

Clinical trials have shown that the lowering of blood pressure in ISH is associated with a decrease in cardiovascular events.[5] Patients with ISH should be treated with antihypertensive drug(s) to reduce the blood pressure to minimize the complications. Older individuals with untreated or inadequately treated ISH require more than a two-fold greater reduction in SBP to attain JNC-VII treatment goals compared to younger patients.[6] Studies have proven that Amlodipine is more effective in reducing the systolic blood pressure in patients with ISH.[7]

The present study evaluated the tolerability and safety of Amlodipine besylate in the treatment of ISH in adult Indian population and was conducted as per ICH GCP guidelines.

METHODS

Patients

Five hundred doctors from all over India recruited 1770 patients with ISH (ISH, SBP ≥ 140 mm Hg) who fulfilled inclusion/exclusion criteria and gave written informed consent to participate in the study. Patients were treated with Amlodipine besylate, at 2.5 – 10 mg/day, p.o (as per the prescribing information). Those with secondary hypertension, malignant hypertension, evidence of organ damage and any other condition which could interfere with the study or expose the patient to unnecessary risks by participation, known hypersensitivity to Amlodipine or similar compounds were excluded.

Study Design

This was a phase IV, multicentric, open labeled, prospective study, conducted in outpatient setup.

Methods

Enrolled patients were prescribed Amlodipine besylate and evaluated frequently till treatment goals were achieved. The treatment success was defined as achieving the SBP < 140 mm Hg and DBP < 90 mm Hg. Efficacy observation was done by frequent monitoring of the patient's blood pressure. Recommendation of JNC VI was followed to measure blood pressure. Time required to achieve the target BP was also assessed.

Patients were allowed to continue medications for any pre-existing or co-existing illnesses that was not contraindicated according to the prescribing information of Amlodipine besylate. Additional antihypertensive medication(s) were prescribed, if required, at the discretion of the investigator, to obtain optimal blood pressure control.

Demographic characteristics such as age, gender, body weight, clinical information on the status of ISH (previously untreated or inadequately treated), co-existing illness, prescription data on concomitant medications with their respective doses and duration of intake, dose and duration of Amlodipine besylate therapy, additional antihypertensives (if any) and attainment of therapeutic goal were recorded. Adverse events reported by the patient, their nature, intensity, outcome and causal relationship to study medication were also documented.

Statistics

Descriptive statistics is given as mean ± standard deviation (SD) for all the demographic and efficacy parameters. Reported adverse events are summarized to assess the safety of the drug. Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations were performed using STATA version 10.1 for Windows (Stata Corp, College Station, TX).

RESULTS

Demography

In this study, 58.74% males and 41.26% females, with a mean age of 61.20 ± 10.33 years were enrolled. Demographic characteristics of the patients who participated in the study are shown in Table 1. Majority of the enrolled patients were untreated (62.97%), while the

rest were previously inadequately treated; Co-existing diseases was present on 42.94% and 59.27% were taking concomitant medications.

Table 1: Demographic Characteristics (n=1770)

Base line features	Mean	S D	Median	Min	Max	95% CI
Age (yr)	61.2	10.33	62	25	92	60.71, 61.68
Body Weight (Kg)	64.15	11.05	64	29	110	63.62, 64.68
Baseline systolic BP(mm Hg)	171	14.81	170	140	230	170.31, 171.69

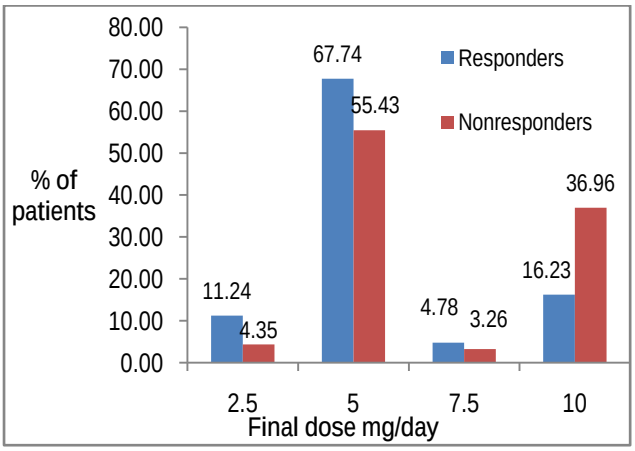

Fig. 1: Therapeutic Response and Final dose

*n=1770

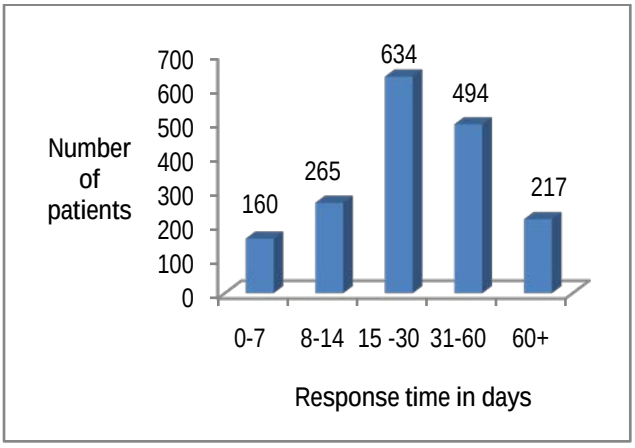

Fig. 2: Response time

Efficacy

Dose

Of 1770 patients, 1217 (72.48%) patients started the therapy at 5mg/day (initial dose). There was a statistically significant difference (p=0.00) in the baseline systolic BP which was higher in those who received 5mg/day as the initial dose in comparison to those who received 2.5 mg/day. The mean SBP was 171.45 ± 13.79 mm Hg in the former group and 166.45 ± 14.49 mm Hg in the latter group. There was a significant association (p=0.00) between the grades of ISH and the initial prescribed dose of Amlodipine besylate, higher dose being prescribed to achieve the therapeutic goal among the ISH patients who were categorized as grade III based on their baseline SBP level.

Previously inadequately treated patients required a higher dose of Amlodipine besylate than untreated patients which was statistically significant (p=0.00). Subsequent increase and reduction (due to adverse events) of the dose was reported in 26.10% and 5.14% of the patients respectively. , 67.32% patients completed the study at a final dose of 5mg/day.

Therapeutic Response

In our study, 93.88% of the patients responded favorably to the treatment. The desired therapeutic response (BP < 140/90mm Hg) was achieved in 64.81% patients in the previously untreated group and 35.19 % in previously inadequately treated group. Fig 1. shows the therapeutic response and the final dose administered to the study group.

Response time:

Mean time required to achieve the therapeutic response was 31.82 ± 25.35 days, [95% confidence interval (CI) 30.62, 33.02]. Desired response was achieved within 14 days in 24.01% patients and 59.83% patients responded within 30 days (Figure 2), indicating an early onset of therapeutic response with Amlodipine besylate in these patients.

Patients who were inadequately treated prior to the study, took a longer time [34.73±24.56 days] to respond than the untreated and the difference was statistically significant (p=0.0004). Patients who received Amlodipine besylate monotherapy responded earlier [31.10±24.69 days] than those who received other antihypertensive agents concomitantly [35.022± 27.919(Mean± SD)] and the difference in response time between these groups was statistically significant.

Safety and Tolerability

There was no serious adverse event or death reported in this study. A total of 282 adverse events reported from 231 patients. The mean duration of AE was 13.79 ± 16.05 days. The incidence of reported adverse events was 15.93%. Pedal edema was the most common adverse event reported (7.46%) followed by headache (2.15%), palpitation (0.62 %) and giddiness (0.56%).

DISCUSSION

ISH, being a poorly diagnosed condition, requires prompt treatment to prevent further complications. Many agents have been in use, individually as well as in combination for the treatment of ISH. Amlodipine has been in clinical use since 1992 and many clinical trials have confirmed the effectiveness and safety in the primary management of ISH.

In the present study, the therapeutic success rate achieved with Amlodipine besylate in patients with ISH was 93.88%. Earlier studies by Calvo et al[7] and Richard Grimm et al [8] have reported therapeutic success rates of 80% and 67% with Amlodipine treatment respectively. Amlodipine besylate also produced an early onset of therapeutic response with 24.11% of patients achieving the target BP within 14 days comparable to the results of the study by Khokhani RC et al.[9] Study by Mariani et al [10] has shown significant reduction in the systolic arterial pressure at the end of third week.

In our study, 67.32 % of patients responded to 5mg/day of Amlodipine besylate. A similar observation has been made by Valcarcel[11] who reported 62.9% of patients achieving BP control with 5mg/day. In another study by Webster and Fowler[12] , amlodipine was found to be highly effective at 5mg/day.

A significant association was noted in this study between the grades of ISH and the initial dose prescribed, with grade III patients requiring higher dose. Further, it was observed that previously untreated patients required lower dose of Amlodipine besylate, compared to inadequately treated patients (p=0.00). There was also an association between the untreated and inadequately treated groups and the initial prescribed dose of Amlodipine besylate.

Adverse events that occurred during the study were as expected and the drug was well tolerated as in the case of previous studies.[11]

Amlodipine besylate was found to be well tolerated in patients with ISH. Earlier studies by Valcarcel[11] and Calvo et al[7] have also reported similar observations about the tolerability profile of Amlodipine. Overall, the results of this study endorse the earlier findings that Amlodipine besylate is effective in the treatment of patients with ISH and is a well tolerated antihypertensive drug.

CONCLUSION

The results of this PMS Study indicate that Amlodipine besylate offers an effective and safe therapeutic option for the management of ISH in adult Indian population, as it is effective and well tolerated and exhibits a good safety profile.

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