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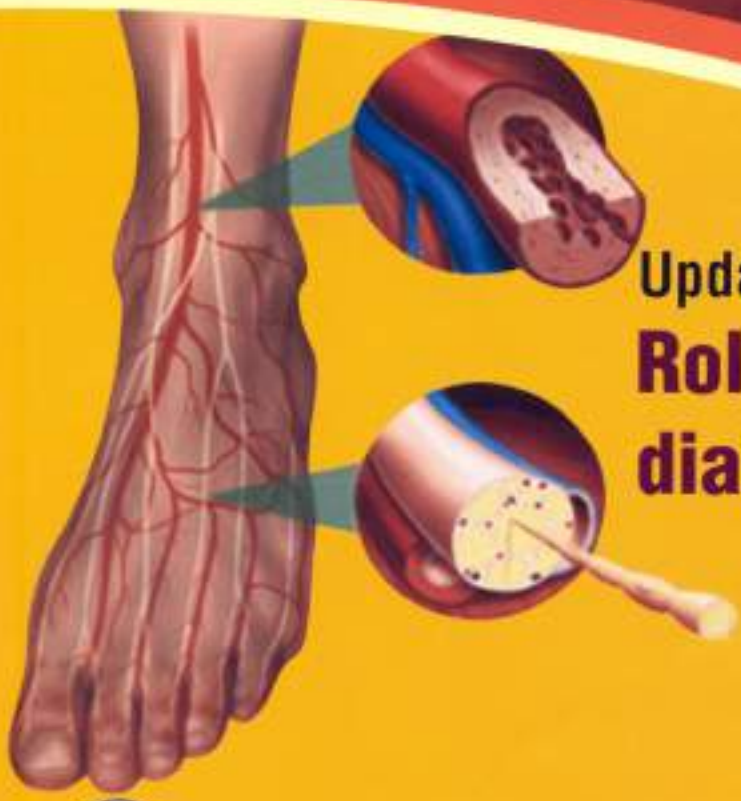

Update curriculum

Role of exercise in diabetes mellitus

Volume 17 I Number 4

Post marketing assessment of the efficacy and safety of S(-) Amlodipine

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BACKGROUND:

Aim: This is a post marketing surveillance carried out to assess the clinical safety and efficacy of S(-) Amlodipine in patients with hypertension. **Materials & Methods:** 81 practicing physicians throughout India collaborated in the recruitment of 235 hypertensive patients over a period of 6 months. Hypertensive patients were administered S(-) Amlodipine (2.5 or 5 mg). The fall in Blood pressure was observed at the end of 30 days. Serious adverse events were also reviewed. **Results:** Significant reduction was observed in the systolic and diastolic blood pressure after treatment with S(-) Amlodipine for a period of 30 days. More than 80% of the patients on S(-) Amlodipine monotherapy achieved the JNC 7 goal in standing, sitting and supine positions. **Conclusion:** These results are reassuring and provide further evidence of the safety and efficacy of S(-) Amlodipine in the management of hypertension. **Key words:** Hypertension, S(-)Amlodipine, Blood pressure, Post-Marketing Surveillance.

INTRODUCTION

Hypertension, a highly prevalent condition, represents the number one underlying cause of death worldwide. It is a well-known major risk factor for organ damage and cardiovascular (CV) disease in both developed and developing countries.[1-3]

Recent reports indicate that nearly 1 billion adults (more than a quarter of the world's population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 2025.[4]

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has published guidelines for the management of hypertension which recommend a target blood pressure of <140/90 mm Hg for all patients with hypertension. Despite an increase in awareness and treatment of hypertension and guidelines outlining anti-hypertensive treatment strategies during the past few decades, only a minority of patients achieve target blood pressure.[5] Thus a major challenge in the treatment of hypertension is inadequate BP control, with only 3–38% of patients worldwide attaining target BP of < 140 / 90 mmHg. Among the various factors contributing to inadequate BP control, efficacy and tolerability of drug treatment seem to play a prominent role.[6]

Among the various classes of pharmacological agents used in treatment of hypertension, Amlodipine, a dihydropyridine calcium channel blocker, is the potential first-line therapy, either alone or in combination with other agents in hypertension management guidelines.[7,8] Peripheral edema, particularly of the lower limbs (incidence ranging from 30.6% - 36.8%),[8,10] is one of the most common adverse effects of dihydropyridine calcium channel blockers and may result in the need for dose reduction or drug withdrawal, both of which can adversely affect antihypertensive efficacy.[7]

To prevent peripheral edema, amlodipine is used in combination with potent and highly selective blocker of the renin–angiotensin system (like ACE inhibitors, ARB, Direct renin receptor inhibitors), to compensate for the arteriolar dilation produced by amlodipine by also dilating the venules, limiting fluid leakage into tissues.[6]

Amlodipine is used therapeutically as a racemic mixture, composed of S and R enantiomers in equal proportion, but with calcium channel-blocking effect confined only to S(-)Amlodipine; R-amlodipine being 1000-fold less active than its S-counter part, it produces long-lasting antihypertensive effect with lesser reflex tachycardia. It maintains and reinforces the pharmacokinetics advantages of amlodipine (higher bioavailability, longer half life, lipophilicity, vascular selectivity etc.).[11] Since S(-)Amlodipine exhibits lesser variability in plasma concentration than the racemate it results in smoother and non fluctuating reduction in blood pressure.[10] Furthermore, the physicochemical properties like charged state at physiologic pH levels, high membrane affinity and lipophilicity that endow anti-atherosclerotic properties on amlodipine are all inherited by S(-)Amlodipine. In addition, it also exhibits enhanced safety and predictability of response in elderly patients.[11] S(-)Amlodipine at half the dose of racemic amlodipine is commercially available in various countries for the treatment of hypertension and angina.[11] Randomized controlled trials of S(-)Amlodipine at half the dose of racemate in the treatment of hypertension, have shown it to be as effective as racemic amlodipine.[14-16] Earlier postmarketing surveillance studies (n=4089) of S(-)Amlodipine have confirmed its antihypertensive efficacy and have also demonstrated that the incidence of peripheral edema is lower with S(-)Amlodipine as compared to racemic amlodipine. Further, the patients with peripheral edema who were switched over from racemic amlodipine to S(-)Amlodipine resolved their edema associated with the racemate, while sustaining the blood pressure control.[13]

The objective of this post-marketing surveillance study of

S(-)Amlodipine was to reconfirm its antihypertensive efficacy and safety profile.

MATERIALS AND METHODS

Study subjects

Physicians throughout India were invited to participate in this study. Eighty one physicians recruited patients with a target number of 4 patients per physician from November 2008 to April 2009.

The targeted patient population was newly diagnosed hypertensives (aged ≥18 years). The study also included patients who could have been on previous drug therapy which was considered inappropriate due to lack of efficacy or side-effects.

Study design

This post marketing surveillance was an open, uncontrolled, prospective observational study wherein patients were evaluated for efficacy, compliance and occurrence of adverse reactions at day 15 and day 30 from the beginning of treatment. Patients were classified according to the severity of hypertension based on the JNC 7 Category. All therapeutic decisions were determined solely by the attending physician. Depending upon the baseline blood pressure values, patients were prescribed S(-) Amlodipine [Eslo] 2.5/5.0 mg orally once daily. The duration of observation was for one month. Medical examinations were performed at 15 and 30 days. At each follow-up visit, standing, sitting and supine blood pressure and pulse rate were measured. Patients' spontaneous reports of any problem whether related to therapy or not were recorded. In accordance with the normal prescribing practice, dosage adjustments were effected by the physician as necessary. All the materials used in this study, including the drugs, were provided by Zuventus Healthcare Ltd.

Data collection

A standardized case report form (CRF) was provided to the doctor where data of each patient was documented over a period of 1 month. Patients' blood pressure values and adverse reactions reported or observed during the study were recorded in the CRF by the participating physicians. Each completed CRF was sent to the Zuventus Healthcare Ltd. for analysis.

Statistical analysis

Data collected during the study were analyzed descriptively and were described by the total number of observations, mean and standard deviation. Efficacy was estimated by measuring the average systolic and diastolic blood pressure before and after treatment. Statistical significance was calculated using paired Student's t-test. Overall 'p' value less than 0.05 was considered as statistically significant. Safety was estimated by measuring the proportion of patients reporting adverse events.

RESULTS

A total of 360 patients were recruited into the study by the physicians. Valid entry data with adequate reporting of demographic data were available for the 235 subjects representing the study population.

Patient characteristics

The demographic data of the 235 patients recruited to the study are shown in Table 1. The mean age of the patients was 52.72 ±(SD) 10.5 years with a range from 18 to 83 years. The duration of hypertension ranged between 0.02 to 20 years with a median of 2.8±(SD) 2.8 years.

Concomitant therapy

The concomitant medication taken by the patients are shown in Figure 1. Only 13 (5.53%) took a concomitant of antihypertensive agents. Among the various anti-hypertensives, 7.69% took ACE inhibitors, 30.77% an ARB, 61.54% took beta-blockers and 53.85% a diuretic.

Efficacy of the treatment regimen:

Reduction in blood pressure

Figure 2, Figure 3 and Figure 4 show the fall in blood pressure over the period of 30 days. The mean systolic and diastolic blood pressure in standing, sitting and supine position in 235 patients who successfully completed 30 day treatment is tabulated in Table 2. Significant reduction was observed in the systolic and diastolic blood pressure after treatment with S(-) Amlodipine for a period of 30 days. It should be noted that only 5.53% of patients were taking other antihypertensive medication in addition to S(-) Amlodipine.

Achieving JNC VII goal blood pressure

As per JNC 7, the treatment goal for individuals with hypertension and no other compelling conditions is <140/90 mmHg. 73.62% (173/235) of the total patients achieved this goal in all the 3

Table 1. Baseline demographic data

		N (235)	%
Age	52.72± 10.5	219	93.19
	Not Stated	16.00	6.81
Sex	Males	151	64.26
	Females	84	35.74
Dose	2.5 mg	152	64.68
	5 mg	62	26.38
	Not Stated	21	8.94
Duration (Yrs)	Less than 1	45	19.15
	Less than 5	99	42.13
	Less than 10	26	11.06
	More than 10	15	6.38
	Not Stated	50	21.28
Severity	Pre-hypertension	6	2.55
	Stage I	96	40.85
	Stage II	133	56.60

Figure 1. Concomitant medication taken by the patients during the observation period

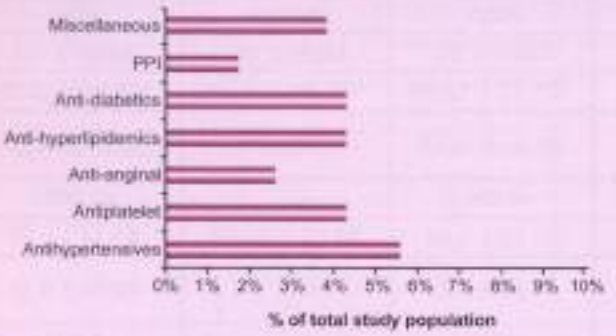


Figure 2. Reduction in BP in standing position

Figure 3. Reduction in BP in sitting position

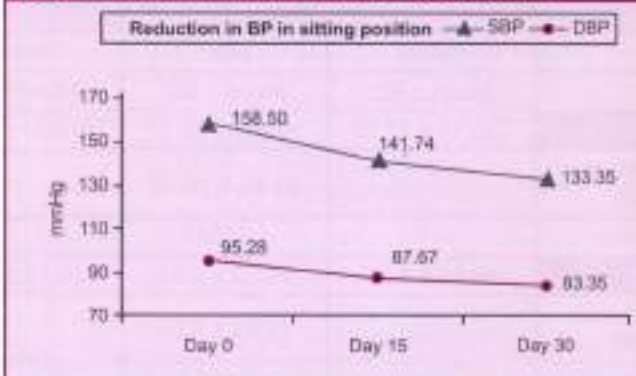
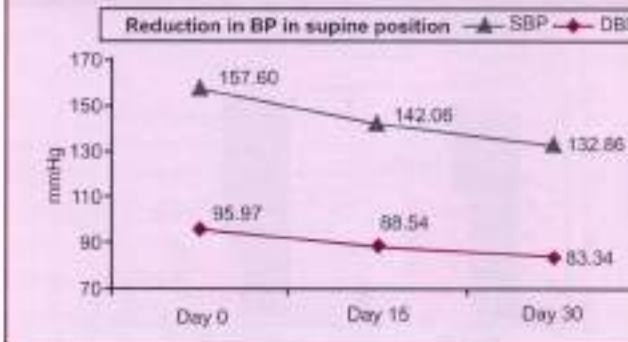


Figure 4. Reduction in BP in supine position



positions, at the end of 30 days of treatment. Subgroup analysis showed that 222 patients were on S(-) Amlodipine monotherapy. 81.08%, 80.63% and 80.18% of these patients achieved the JNC goal in standing, sitting and supine positions respectively. Among the 13 patients who took other anti-hypertensive drug concomitantly, 69.23% achieved the JNC goal.

Among the 222 patients on S(-) Amlodipine monotherapy, 164 achieved the JNC goal simultaneously in all the 3 positions. Among these patients, 3.66% had prehypertension before treatment while 51.83% had Stage I hypertension and 44.51% had Stage II hypertension.

Resolution of associated symptoms

Most patients with hypertension have no specific symptoms referable to their blood pressure elevation. In this study, other associated complaints which maybe related to elevated blood pressure reported by the patients were recorded. The resolution of these symptoms during the treatment with S(-) Amlodipine is shown in Figure 5.

Safety assessment:

91.49 % of the patients did not report the incidence of ankle edema over a period of 30 days. On the basis of clinical data available, other adverse events reported in less than 5% of the patients included anxiety (0.43%), anorexia (0.43%), irritation (0.43%), headache (2.13%) and facial flushing (2.13%).

DISCUSSION

As with the previous postmarketing surveillance studies on antihypertensive drugs, this study is an observational cohort study designed to detect unsuspected adverse reactions. Data on efficacy are incidental. However, in the overall context of the risk-benefit of therapy, it is important to select a dosing schedule that is both appropriate and efficacious. In this cohort, adequate control of blood pressure was achieved and mean blood pressure was significantly reduced (Table 2) in the 235 patients who successfully completed 1 month treatment. The majority (75.74%) received S(-)Amlodipine alone.

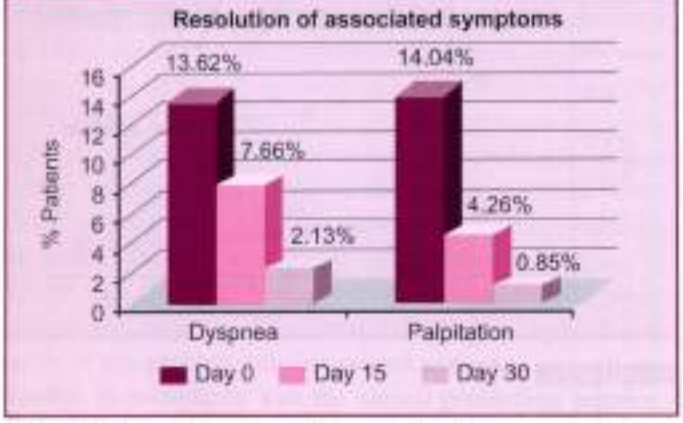
The reduction in blood pressure observed during this study was similar to those observed in previous studies conducted on S(-)amlodipine.[14,15,17] Although, the reduction of BP was similar, the duration of treatment was shorter as compared to the previous studies.[14,15]

In this study, two strengths of S(-)amlodipine were prescribed by the physicians. It was observed in our study that out of the 152 patients who received 2.5 mg of S(-)amlodipine, 6 had prehypertension, 70 had Stage I, while 76 had Stage II hypertension. Among these, the JNC goal was achieved by 100% patients in the prehypertension group, 87.14% in Stage I and 57.89% in the Stage II group. Likewise out of the 62 patients who received 5 mg of S(-)Amlodipine, 13 had Stage I while 49 had Stage II hypertension. 92.30% of the patients in Stage I group were able to achieve the JNC goal while in the Stage II group it was only

Table 2. Mean systolic and diastolic blood pressure values before and after treatment

	STANDING		SITTING		SUPINE	
	Before	After	Before	After	Before	After
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
SBP	159.12 ± 17.53	133.64 ± 12.31	158.50 ± 17.91	133.35 ± 12.36	157.60 ± 17.46	132.86 ± 12.02
Reduction in BP		25.48 ± 14.38		25.15 ± 15.49		24.74 ± 14.83
p value		<0.0001		<0.0001		<0.0001
DBP	96.94 ± 9.25	84.13 ± 6.24	95.28 ± 9.13	83.35 ± 5.98	95.97 ± 10.99	83.34 ± 6.26
Reduction in BP		12.81 ± 7.84		11.93 ± 7.83		12.63 ± 9.45
p value		<0.0001		<0.0001		<0.0001

Figure 5. Resolution of associated symptoms



52.27%. Although these results do not signify any major finding, it reinforces the use of 2.5 mg of S(-)Amlodipine as an initial single agent in the treatment of hypertension, not only in mild to moderate hypertension but also in severe hypertension. Previous studies have demonstrated that 2.5mg of S(-)Amlodipine is equivalent in its efficacy and tolerability when compared to 5mg Amlodipine.[15,16] The observations in this study in conjunction with previous studies show that a dose of 2.5mg of S(-)Amlodipine may be sufficient for the treatment of hypertension. Increase in dose should be considered in case of inadequate blood pressure control. The new BP guidelines (to be published in the October 2009 issue of the *Journal of Hypertension*) by European Society of Hypertension (ESH) outlines that rather than emphasizing which antihypertensives should be used first-line, second-line, etc, it is advisable to tailor the therapy to individual patient circumstances.[18] The data from this study shows that S(-)Amlodipine may have a niche role to play in such customized therapy.

Generally, addition of a second drug from a different class is initiated when the use of a single agent in adequate doses fails to achieve the goal. Among the 13 patients who took other anti-hypertensive drug concomitantly, 69.23% achieved the JNC goal. Thus it only adds on to existing data of the utility of S(-) Amlodipine in combination therapy of hypertension.

The incidence of ankle edema is higher with treatment of racemic amlodipine. Clinical studies have tended to give low estimates of incidence of ankle edema with S(-)Amlodipine. Overall incidence of edema is 1.39% as against the reported incidence ranging from 1.7 to 32% with racemic Amlodipine.[3] This study found an overall incidence of 8.51%. The comparatively high reporting of this problem obtained in this postmarketing study tends to support the relative bias favoring reporting of such well known associations as this. Minor events may or may not be recorded by individual practitioners and reporting is biased towards adverse reactions known or suspected of being drug-related. Serious events, particularly life threatening and fatal events, are subject to less bias in ascertainment.

Although the reduction of BP observed in this study was statistically significant, the observed sample size was small. Hence further observational studies involving larger population will further validate the observations of this study.

In conclusion, this postmarketing surveillance of S(-) Amlodipine confirmed its antihypertensive efficacy and showed that the incidence of peripheral edema is very low with S(-) Amlodipine compared to racemic amlodipine. In the light of its efficacy and favorable tolerability profile, S(-)Amlodipine used alone or in combination with other antihypertensive drugs, is a valuable treatment option in the management of hypertension.

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