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QUALITY AND COST WISE EVALUATION OF AMLODIPINE, MANUFACTURED BY LOCAL PHARMA INDUSTRIES TO THAT OF A MULTINATIONAL, IN THE HYPERTENSIVE PATIENTS

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ABSTRACT:

An attempt to evaluate and testify the blood pressure lowering effect, tolerance and the impact of the price to promote patient's compliance and market of `Amlodipine', an antihypertensive calcium antagonist, manufactured by two local and one multinational pharma industry, has been made.

The study was carried out under a clinical trial on 33 hypertensive patients and 18 normal healthy subjects on recommended dose (5 mg) of each, branded with different names for six consecutive weeks.

The findings of the study show that at the end of clinical trial, one of the local product has produced a highly comparable significant ($p < 0.001$) fall in blood pressure as well as serum cholesterol levels with 80% tolerance in the hypertensives to that of normal controls.

So far the price factor of the products is concerned one of the local product was found to be cheaper than that of the multinational whereas the second local product, though cheapest showed poor performance with more side effects.

INTRODUCTION

Hypertensive is the most common chronic medical ailment in the developed world and occurs in 20-30% of the adult population (Beevers 1995) and it is reported that in Eastern Mediterranian Region its prevalence is about 25% and is increasing day by day (Alwan 1993). This has increased the risk of vascular damage leading to cardiac, renal and cerebrovascular morbidity and mortality (Alwan 1996). To prevent morbidity and mortality as well as to maintain blood pressure below the prescribed limits of hypertension i.e. 140/90 mmHg (Nilsson 1997) anti-hypertensive drugs are prescribed when non-pharmacological measures like diet, exercise and other similar remedies fail to bring a reduction in the blood pressure. Since several different types of anti-hypertensive agents are available in the market and since monotherapy has been proposed to be preferable (JNC VI 1997), the challenge for physicians is to select the most accurate, safe and cost-effective drug to treat his patient (Matu and Ahson, 1993).

Calcium antagonits, one of the potent anti-hypertensives of the present times on the basis of their highly selective action on peripheral vascular and cardiac tissues are used commonly for the treatment of myocardial ischemia and hypertension. These drugs are currently available in 3 classes viz: dihydropyridines (e.g. nifedipine, amlodipine,

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felodipine), phenylalkylamines (e.g. verapamil) and benzathiazepines (e.g. dilitazem) and are reported to differ in their pharmacological profile and safety (Knoll and Luscher, 1998).

The safety in the treatment of hypertension can only be seen in relation to efficacy which has now come to be not just blood pressure reduction but improve- ment in hard-end points including mortality (Opie, 1997). Amlodipine has been reported to possess most of the qualities like decrease in smooth muscle tone and vascular resistance, shorter half life and intrinsic naturetic effect etc (Mycek et al., 1997) a potent and safe anti-hypertensive should contain (Companies in the News 1990). Since amlodipine is being manufactured locally by various pharmaceutical industries and marketed with different brand names, our objective of the present study was to evaluate and testify 2 brands of locally manufactured amlodipine and compare their quality, safety and cost-effectiveness to the product of a multi-national.

PATIENTS AND METHODS

Due to the lack of facilities to testify the quality of the drugs through bio-availability and / or bioequivalence tests, our study was restricted to a clinical trial conducted on the patients visiting the out patient department (OPD) in Red Crescent Cardiac Hospital and CCU Latifabad, Hyderabad (Sindh). However proper care had been taken to observe and record clinical changes perfectly and undertaken other laboratory procedures pre- and post- trial tests and compare the results under trial.

Patients Selection

33 clinically diagnosed patients (16 males, 17 females) having their blood pressure more than 140/90 mmHg (systolic / diastolic) with their BP between WHO's prescribed limits i.e. 120/80 were screened and 18 normal healthy volunteers were subjected to participate, on their own consent, in the six week long clinical trial under the supervision of a consultant cardiologist. The following criteria were used to include or exclude the patients in the study.

Inclusion Criteria

i) The study included adults with hypertension (Grade I, II, III) as per having their BP within the WHO (Alwan 1996) prescribed limits and criteria.
ii) 18 normal healthy controls with no family history of hypertension.
iii) The patients and control subjects were of either sex and above 21 years of age.

Exclusion Criteria

i) Patients with target–organ–damage and on other calcium antagonists.
ii) Pregnant and lactating females.
iii) Patients with diabetes.

Table 1
Average blood pressure in normotensives and hypertensives before and six weeks after the administration of Amlodipine

Mean Blood pressure ± SEM (mm Hg)

		Before		After	
		Systolic	Diastolic	Systolic	Diastolic
Drug: 1	Normotensives (06)*	120.0 ± 3.0	82.0 ± 1.5	118.0 ± 1.5	81.5 ± 1.5
	Hypertensives (12)*	153.0 ± 4.0	106.0 ± 3.0	125.0 ± 3.0	84.0 ± 2.0
Drug: 2	Normotensives (06)*	119.5 ± 3.0	80.0 ± 1.0	120.5 ± 3.0	80.0 ± 2.0
	Hyperensives (11)*	158.0 ± 3.5	106.5 ± 1.5	145.5 ± 5.0	100.0 ± 7.0
Drug: 3	Normotensives (06)*	125.0 ± 3.0	74.0 ± 1.5	123.5 ± 2.0	73.7 ± 1.0
	Hypertensives (10)*	164.0 ± 5.0	106.0 ± 3.0	127.0 ± 2.0	83.5 ± 1.0

Table 2
Blood/urine data showing pre- and post- drug values of various biochemical parameters

* No. of subjects

		Pulse Rate Beats/min		Blood Sugar mg/dl (Random)		Blood Choleste-rol mg/dl		Blood Urea mg/dl		Blood Uric Acid mg/dl		Blood Creatinine mg/dl		Sp. Gravity (urine)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Drug: 01	Normotensives (06)* Hypertensives (12)*	71.0 80.0	72.0 74.5	105.0 110.0	107.0 101.0	134.0 213.0	126.0 179.0	16.42 27.13	15.70 24.73	4.37 7.21	4.21 5.89	0.513 0.42	0.510 0.45	1.010 1.019	1.010 1.010
Drug: 02	Normotensives (06)* Hyptertensive (11)*	74.4 78.0	77.1 76.5	112.0 116.0	120.0 116.0	141.0 177.0	135.6 162.0	17.39 28.83	17.12 30.22	4.19 5.77	4.12 5.41	0.73 0.9	0.68 0.8	1.012 1.022	1.015 1.020
Drug: 03	Normotensives (06)* Hypertensives (10)*	73.0 74.5	70.6 71.5	120.0 133.0	125.0 127.0	145.0 205.0	140.0 193.0	16.19 19.84	15.91 21.38	4.37 5.57	4.10 4.67	0.63 0.416	0.51 0.40	1.015 1.015	1.010 1.014

Table 3
Overall assessment of various brands of Amlodipine tolerance in patients, who completed six week-long clinical trial

Brand	No. of Patients responded well	No of Patients complained for side effects	Percent tolerance
Drug: 01 (Local Product)	10	02	80
Drug: 02 (Local Product)	04	07	36
Drug: 03 (Multinational Product)	08	02	80

Table 4
Data showing dose schedule and incidence of side effects of Amlodipine products (manufactured by different pharmaceutical industries) in the patients under trial

Product	Dose	Side Effects	Incidence Number (%)
Drug: 01 (12)*	5 mg	Palpitation Flushing	01 (8%) 01 (8%)
Drug: 02 (11)*	10 mg	Palpitation Constipation Edema (mostly on ankle and wrist)	02 (18%) 06 (55%) 07 (64%)
Drug: 03 (10)*	5 mg	Constipation Palpitation	02 (20%) 01 (10%)

*No. of subjects

Table 5
Cost of different products of Amlodipine, manufactured by various pharmaceutical industries in Pakistan, used in the clinical trial

Brand	Adult usual Dosage	Formulation	Cost *(in rupees)
Drug: 01	5 mg 10 mg	Tablet Not manufactured	225.00 --
Drug: 02	5 mg 10 mg	Tablet Tablet	76.50 148.50
Drug: 03	5 mg 10 mg	Tablet Tablet	397.50 777.00

*Cost of the patients for 30 day's treatment of hypertension based on retail price as recommended by the manufacturer.

like medical history, examination ECG supine blood pressure measurements (average of 3 readings) etc. prior to start blood and urine samples were obtained for complete and detailed laboratory examination. Afterwards, the patients were divided randomly into 3 groups and were kept on different amlodipine brand therapy on the recommended dose of 5 mg per day as follows:

Group A on Drug: 01 (Amlod: local product: 5mg) 12 patients + 06 normal controls.

Group B on Drug: 02 (Sofvasc: local product: 5 mg and 10 mg) 11 patients + 06 normal controls.

Group C on Drug: 03 (Norvasc: multinational product: 5 mg) 10 patients + 06 normal controls.

Follow-Up

To assess the anti-hypertensive effect, the patients were advised to attend the OPD for regular check ups, every week. During these visits the blood pressure, pulse (heart) rate and adverse reactions reported by the patients were noted.

Statistical Analysis

Level of significance of different parameters between patients and normal volunteers was determine using Mann Whitney's formula.

RESULTS

The post-drug findings (Table 1) reveal that the two brands of amlodipine i.e. drug: 01 and drug: 03 have produced a significant fall ($p < 0.001$) in both systolic and diastolic blood pressures. In contrast, drug: 02 did not respond with 5 mg but when increased the dose to 10 mg it produced an irregular (weekly) and a non-significant decrease in the blood pressure, while the normotensives showed no change in their blood pressure levels.

Serum and urinary laboratory findings indicate knowledge of other CV factors and clinical conditions that may influence the prognosis and treatment, of pre- and post-trial, as mentioned in table 2. When compared significant reduction of cholesterol with all the drugs in the patients as compared to the normal controls were observed. So far the other parameters are concerned all showed a slight fall or remained unchanged.

When amlodipine was assessed in terms of percentage tolerance (that is; no unwanted effect) same drugs (drug no. 01 and no.3) again were found to be quite comparable as can be seen in table 3, and were well tolerated by majority of patients (80%), evaluated. Conversely drug: 02 showed a very poor response with serious side effects. The details of the side effects experienced by the patients are reported in table 4 and one can understand that all the products exhibited the reported side effects with variable severity. Since the choice of drugs depends on associated disorders their cost and side effects profile and since the 3 brands belong to the same compound, the cost to provide medication, accordingly was then calculated and a table comprising the cost of the product was constructed (table 5) on monthly basis. The data reveals that the product manufactured by the local firms are cheaper than that of multinational.

DISCUSSION

As life expectancy decreases with increased blood pressure, antihypertensive therapy is considered to be a method to prevent the development of complications that cause morbidity and shorten life (Collins et al., 1990). In recent years besides others, calcium antagonists have been extensively used as potent anti hypertensive agents because they are more versatile than most previous vasodilators on the basis of their favourable accompanying effects on heart and kidney without deleterious effects on metabolic functions (Nilsson 1997).

In present investigation; an effort was made to evaluate and compare the efficacy,

safety and cost effectiveness of different brands of amlodipine, a calcium channel blocker, being manufactured and marketed as Amlod (drug: 01), Sofvasc (drug: 02) and Norvasc (drug: 03) in this country and it is evident from the data that the products produced by local firms are much cheaper than the one manufactured by the multinational.

On the basis of the efficacy, tolerance and adverse effects experienced in this study, drug: 01 a local product has quality wise proved to be at par with that of drug: 03, an internationally recognized potent drug, but cheaper and cost effective. Hence, local product (drug: 01) could be more acceptable to poor and les privileged people of developing and under developed countries than the one produced by a multinational. Another local product (drug: 02) though cheapest and more cost effective, even when used in double dose could not come up to that level because of poor performance and more side effects.

This study therefore seems to be an attempt to testify the efficacy of drug manufactured by our local pharma industry and also to reduce if possible, the economic burden from our population to some extent as our community faces a major problem of compliance, compounded by lack of education and poverty.

It is therefore proposed that such comparative studies should be conducted regularly to strengthen and promote our local pharmacy industry to bring their products equally potent and effective to that of a multinational. This would save heavy foreign exchange of the country being spent every year and also would provide a cheaper therapy to our poor nation.

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