

Adverse drug effects monitoring of amlodipine in a tertiary care hospital

M. Venkateswaran¹, M. Poornima¹, C. Vinoth Kumar^{2*}

¹Department of Pharmacology,
Govt Mohan Kumaramangalam
Medical College, Salem,
Tamilnadu, India

²Department of Pharmacology,
Govt Sivagangai medical
College, Sivagangai, Tamilnadu,
India

Received: 18 April 2018

Revised: 28 April 2018

Accepted: 14 May 2018

***Correspondence to:**

Dr. C. Vinoth Kumar,
Email: vinothcdr@gmail.com

Copyright: © the author(s),
publisher and licensee Medip
Academy. This is an open-
access article distributed under
the terms of the Creative
Commons Attribution Non-
Commercial License, which
permits unrestricted non-
commercial use, distribution,
and reproduction in any
medium, provided the original
work is properly cited.

ABSTRACT

Background: Amlodipine have been widely used drug for the treatment of Hypertension. It has many beneficial effects and less side effects. But, only very few adverse effects of Amlodipine have been documented and many were not reported. So, this study will bring out the possible adverse effect of Amlodipine.

Methods: This study included 100 patients with hypertension who are taking amlodipine only. Patients who were willing to participate in the study were given a questionnaire containing demographic data and adverse drug profile of amlodipine. The symptoms of adverse drug reaction were documented. They were also asked about the other symptoms they are having, other than the questionnaire. The causality assessment was done by WHO assessment scale and severity by using modified Hartwig seigel severity assessment scale.

Results: This study showed that most of the patients belong to 51-60 years age group. Mostly they were females, and many were having disease for less than a year. Most of the patients developed adverse drug reaction. Many patients had more than one adverse drug reaction. The commonest adverse effect were fatigue, palpitation, dizziness, insomnia, headache, joint pain, light-headedness, somnolence, nausea, flushing abdominal pain, tremor, leg pain, neck pain, back pain and edema. The adverse drug reaction(ADRs) mostly belongs to possible category and were mild.

Conclusions: Most of the patients who were taking amlodipine had atleast one adverse drug reaction during their treatment period. It is mild, needs dose adjustment and healthy life style modification.

Keywords: Adverse drug reaction, Amlodipine, Causality assessment, Hypertension

INTRODUCTION

Hypertension is well established as a major risk factor for cardiovascular disease. Recent studies have shown that hypertension is present in 25% urban and 10% of rural subjects in India. It is the attributable cause for 57% of stroke and 24% of coronary heart disease deaths in India. Present estimates suggest that a 2mmHg population- wide decrease in systolic blood pressure can lead to prevention of more than 151,000 stroke and 153,000 coronary heart disease deaths in India.¹ The hemodynamic hallmark of essential hypertension is an increased total peripheral

resistance, the logical treatment choice is a drug that promotes arteriolar vasodilatation.²

One of the oldest groups of anti-hypertensives, calcium channel blockers were first introduced over 35 years ago initially for coronary heart disease (CHD), but they soon gained wide recognition for their efficacy in hypertension. The initial indication, besides hypertension also included angina, peripheral vascular disease and some arrhythmic conditions. Among the calcium channel blockers(CCB), Amlodipine is a long acting, lipophilic, third generation dihydropyridine(DHP) calcium channel antagonist. It exerts its action through inhibition of calcium influx into

vascular smooth muscle cell and myocardial cells which results in decreased peripheral vascular resistance(PVR).³

It has a pharmacokinetic profile that set it apart from other calcium antagonists. Differential features include a slow onset of action, a prolonged effect, high bioavailability and relatively minor differences in peak to trough plasma levels.⁴ The slow onset of action is related to a prolonged hepatic transfer rate and a slow rate of association with binding sites in L-type Ca⁺⁺ channels. Conversely, the extended duration of action of amlodipine results from slow elimination from the plasma and a slow rate of dissociation from binding sites. Resultant beneficial effects include an absence of reflex tachycardia, unchanged plasma catecholamine levels and renin activity, and a once daily treatment schedule.⁴

Because of its vascular selectivity, amlodipine does not exert a cardio-depressant effect at clinically relevant doses and does not cause bradycardia. Vascular selectivity results in increased coronary and renal blood flow but an overall reduction in peripheral vascular resistance. Thus, the pharmacodynamic and pharmacokinetic properties of amlodipine provide the basis for its effective use as a once-daily treatment in the management of patients with a variety of cardiovascular disorders, including angina pectoris, hypertension and vasospastic angina, with a minimal incidence of adverse events.⁴

Apart from reducing total peripheral resistance, Amlodipine significantly reduced non-fatal myocardial infarction by 26% and stroke or transient ischemic attack by 50%. Amlodipine increased NO production in failing hearts which may be the mechanism for its beneficial effects in heart failure which is not a feature shared by other members of the CCB.³

Amlodipine treatment has been associated with an impairment in the progression of atherosclerosis at both coronary and carotid levels.⁵ The reason for amlodipine's anti-atherosclerotic effect is enhancement of NO production.³ Other mechanism of atherosclerosis like oxidative stress, LDL oxidation and aggregation have been shown to be modified by amlodipine. Studies have shown that amlodipine inhibited oxidative damage to lipids associated with cellular membranes and lipoprotein particles. This anti-oxidant activity of amlodipine was attributed to both its high lipogenicity and its chemical structure that quench the free radical reaction. Finally, other vascular actions of amlodipine included inhibition of vascular smooth muscle cell proliferation and matrix metalloproteinase modulation, all actions can be related with anti-atherosclerotic effects.⁵

The major adverse reactions with amlodipine can be grouped in the following categories:

1. Vasodilation that is characterized by headaches, flushing, palpitations, peripheral edema

2. Gastro-intestinal effects such as constipation, diarrhoea and nausea.²

Among these, peripheral edema is probably the most troubling side effect of CCB therapy. It is not on the basis of salt and water retention, because this drug is intrinsically natriuretic.⁶

Because of these beneficial effects and low side effect profile, amlodipine is considered as first line agent in the treatment of hypertension.

ADR as defined by WHO, "any response which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for the modification of the physiological function."⁷

Although it causes less adverse effect, only very few adverse effects of amlodipine has been documented and many were not reported. Few can lead to discontinuation of the therapy itself like severe edema. Few peoples neglect the adverse effect and think that it may be due to the disease process or due to the other causes except when they are asked specifically about it.

So, this study will bring about the possible adverse effect of amlodipine and a good understanding of adverse effect can improve the patient compliance and to take steps to reduce it in future.

METHODS

The study was conducted after getting approval from institutional ethical committee. This Prospective, Observational study was conducted in the Hypertension OP of Medicine department over a period of one month (Table 1). 100 patients fulfilling the inclusion and exclusion criteria were enrolled in the study (Table 2).

Table 1: Methodology.

Study design	Open label, prospective, observation study
Study population	Patients attending hypertension OP department
Study centre	Hypertension clinic, Department of Medicine, Govt. Mohan Kumaramangalam Medical College
Sample size	100
Study duration	One month

They were explained about the study purpose in their local language. Written informed consent was obtained from those who were willing to participate in the study. If the patient could not understand the purpose of the study, the same was explained to their attenders/relatives and written informed consent was obtained from them. The ADR data

for Amlodipine were collected through a questionnaire (Table 3).

Table 2: Inclusion and exclusion criteria.

Criteria	
Inclusion criteria	Hypertensive patients who are taking amlodipine alone for atleast 3 months
	Age from 30-60 year
	Both gender
	Patients who are willing to give informed consent
Exclusion criteria	Patients who are taking other anti-hypertensive drugs
	Patients with other chronic systemic illness
	Patients not willing to give informed consent

Causality assessment of the Adverse drug effects was done by establishing the temporal association of drug use with adverse drug reaction using WHO Causality assessment scale. Severity was assessed by using modified Hartwig siegel severity assessment scale.⁸

Data were entered in excel spreadsheet and descriptive statistics was used to analyze the data.

Table 3: Study questionnaire.

Name	
Age	
Address	
Sex	M/F
Duration of hypertension	
Any other complication of hypertension	
Other concomitant drug intake	
Do you have the following symptoms?	
Edema of ankles and feet	O yes O no O Don't know
Dizziness	O yes O no O Don't know
Palpitation	O yes O no O Don't know
Flushing	O yes O no O Don't know
Headache	O yes O no O Don't know
Lightheadedness	O yes O no O Don't know
Fatigue	O yes O no O Don't know
Nausea	O yes O no O Don't know
Abdominal pain	O yes O no O Don't know
severe drowsiness	O yes O no O Don't know
Other symptoms if any,	

RESULTS

There were 1568 patients screened, 100 patients who fulfilled the inclusion criteria were analyzed.

Table 4 shows 82% of patients have adverse drug effect with amlodipine use and 18 % of the patients taking Amlodipine had no ADR.

Table 4: Occurrence of adverse drug reaction (ADR).

Patients with / without ADR	Number of patients	Percentage (%)
Patients with ADR	82	82%
Patients without ADR	18	18%
Total	100	100%

Table 5 shows the pattern of ADR with Amlodipine. Fatigue (21.9%) was the most common adverse drug effect followed by palpitation (13.9%), dizziness (12.6%), insomnia (12.6%), headache (11%), joint pain (9.2%), light headedness (5.5%), somnolence (4.7%), nausea (2.1%), flushing (1.6%), abdominal pain (1.3%), tremor, leg pain, neck pain, back pain (0.8%) and edema (0.4%). Apart from the Adverse effects mentioned in the questionnaire, patients mentioned the following effects after taking Amlodipine - Somnolence, insomnia, joint pain, tremor, leg pain, neck pain and back pain.

Table 5: Pattern of adverse drug reactions.

Sr. no	Name of ADR	Number of ADRs	Percentage
1	Edema	1	0.4%
2	Dizziness	30	12.6%
3	Palpitation	33	13.9%
4	Flushing	4	1.6%
5	Headache	26	11%
6	L Headedness	13	5.5%
7	Fatigue	52	21.9%
8	Nausea	5	2.1%
9	Abdominal pain	3	1.3%
10	Somnolence	11	4.7%
11	Insomnia	30	12.6%
12	Joint pain	22	9.2%
13	Tremor	2	0.8%
14	Leg pain	2	0.8%
15	Neck pain	2	0.8%
16	Back pain	2	0.8%
Total		238	100%

Table 6 shows the distribution of ADRs 21.9% patients have 2 ADRs, 18.9% patients have 3ADRs,18.5% patients have 4 ADRs, 12.6% patients have 5 ADRs and 6 ADRs, 8.8% patients have 7ADRs, 6.7% patients have 1 ADRs.

Table 7 shows the severity assessment of Adverse Drug Reaction. 47.5% were categorized as mild, 52.5% were categorized as moderate and 0% as severe adverse drug reaction.

Table 8 shows the Causality Assessment of Adverse Drug Reaction. 55.1% of ADR belongs to possible category,

44.5% of ADR belongs to probable category, and 0.4% of Adverse drug reaction belongs to certain category.

Table 6: Distribution of ADRs in patients.

Number of ADRs in patients	Number of patient	Total number of ADRs	Percentage (%)
1	16	16	6.7
2	26	52	21.9
3	15	45	18.9
4	11	44	18.5
5	6	30	12.6
6	5	30	12.6
7	3	21	8.8
Total	82	238	100

Table 7: Severity assessment.

Assessment category	Number of ADRs	Percentage (%)
Mild	113	47.5%
Moderate	125	52.5%
Severe	0	0%
Total	238	100%

Table 8: Causality assessment.

Assessment category	Number of ADRs	Percentage (%)
Certain	1	0.4%
Probable	106	44.5%
Possible	131	55.1%
Total	238	100%

DISCUSSION

Amlodipine have been widely used drug for the treatment of hypertension. It is an effective antihypertensive drug, providing smooth 24hr blood pressure control without orthostatic hypotension, and that it is well tolerated as monotherapy and in combination with other antihypertensive drugs.⁹ They are effective as single-drug therapy in approximately 60% of patients in all demographic groups and all grades of hypertension.¹⁰

In this study, 100 patients were evaluated for adverse drug reaction. Out of which, majority of them belongs to age group of 51-60 years and females were predominant in this study. Most of the patient were having diseases of one year and less than one year duration. This implies that the first line management of hypertension is amlodipine. The dosage prescribed for these patients was amlodipine 5mg once daily.

Among 100 patients who were on amlodipine, 82 patients developed atleast one adverse drug reaction (82%). The most commonest adverse effect was fatigue (21.9%)

followed by palpitation (13.9%), dizziness (12.6%), insomnia (12.6%), headache (11.0%), joint pain(9.2%), light-headedness (5.5%), somnolence (4.7%), nausea (2.1%), flushing (1.6%), Abdominal pain (1.3%), tremor, leg pain, neck pain, back pain (0.8%) and edema (0.4%).

Many patients have three adverse drug reactions and more than that. Out of which fatigue, insomnia, palpitation, dizziness, headache were more common. About 55% of ADRs comes under possible category of WHO assessment scale

These adverse effects can be minimized if the Amlodipine is given at bedtime and at lower doses (2.5 or 5mg per day).³ Patient should also be advised to take timely and adequate meals with fruits containing potassium, so that the incidence of nausea, vomiting, constipation can be reduced.

CONCLUSION

Majority of patients taking amlodipine developed more than one adverse drug reaction which may be dose related. Fatigue and insomnia comes under possible category, dizziness and palpitation comes under probable category of WHO causality assessment. Therefore, dose adjustment and lifestyle modification can reduce the adverse effects of amlodipine.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

- Gupta R, Gupta S. Hypertension in India: Trends in Prevalence, Awareness, Treatment and Control. *RUHS J of Hea Scien.* 2017;2(1):40-5.
- Russell P. Side Effects of Calcium Channel Blockers. *Journal of the American Heart Association.* 1988;11(3):42-4.
- Fares H, Di Nicolantonio JJ, O'Keefe JH, Lavie CJ. Amlodipine in hypertension: a first -line agent with efficacy for improving blood pressure and patient outcomes. *Open Heart.* 2016;3(2):1-7.
- Nayler WG. Amlodipine - An Overview. *Clinical Drug Investigation.* 1997;3(1):1-11.
- Alejandro de la S. Amlodipine In The Prevention And Treatment Of Cardiovascular Disease. *European Cardiovascular Disease.* 2007;3(1):66-8.
- Sica DA. Calcium Channel Blocker-Related Peripheral Edema: Can It Be Resolved? *The J of Clin Hyperten.* 2003;5(4):291-5.
- International drug monitoring: the role of national centres. Report of a WHO meeting World Health Organ Tech Rep Ser. 1972;498:1-25.
- Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug

reactions. *Am J Hosp Pharm*. 1992 Sep;49(9):2229-32.

9. Julius S. Amlodipine in hypertension: an overview of the clinical dossier. *J Cardiovasc Pharmacol*. 1988;12(7):27-33.
10. Sutters M. Systemic Hypertension. In: Maxine A. Papadakis, Stephan J. Mcphee. *Lange's Current*

Medical Diagnosis and Treatment. 55th Edition. McGraw-Hill; 2016:435-467.

Cite this article as: Venkateswaran M, Poornima M, Kumar CV. Adverse drug effects monitoring of amlodipine in a tertiary care hospital. *Int J Basic Clin Pharmacol* 2018;7:1078-82.