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Antihypertensive Activity and ADR Survey of Amlodipine and Telmisartan in Hypertension

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Kiran S. Gaykwad*, Abhay A. Nirmal, Gokul M. Davkar, Ajinkya M. Sonune

Shri Sant Gajanan Maharaj College Of Pharmacy, Buldana, Maharashtra 443001 India.

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ABSTRACT

Aim: Antihypertensive activity and ADR survey of amlodipine and telmisartan in hypertension. **Objectives:** To identify the combination activity of amlodipine and telmisartan in hypertensive patients. To know drug interaction with amlodipine and telmisartan. To find out other possible side effects or actions other than hypertension. To find out the therapeutic failures of combination treatment. To find out clinical trial data. To find out fixed dose combinations and dose frequency. Review all the information about their mode of action, pharmacological properties, general properties, chemical properties and detailed information about amlodipine and telmisartan. There is much more evidence that blood pressure (BP) control significantly reduces the risk of future cardiovascular events in patients with essential hypertension. However, BP control is strict and difficult to maintain, half of hypertensive patients fail to control BP on single-drug therapy. (3) Therefore, current guidelines recommend combinations of antihypertensive drugs that have complimentary modes of actions for the treatment of patients with acute or moderate hypertension. In this study, we examined in hypertensive patients controlled by the combination treatment with 5 mg amlodipine plus 40 mg telmisartan. Amlodipine, a third-generation dihydropyridine CCB, is a racemic mixture consisting of the R-enantiomer and S-enantiomer in a 1:1 ratio Amlodipine is an oral dihydropyridine calcium channel blocker. Amlodipine is available as amlodipine besylate, initially approved in 1987 by the Food and Drug Administration (FDA) Amlodipine is primarily administered orally and is available in 2.5 mg, 5 mg, and 10 mg tablets, amlodipine has the longest half-life at 30 to 50 hours. The benefit of such a long half-life is the ability to have once-daily dosing. (3) Telmisartan is an ARB, with a selective type 1 receptor blockade effect. The antihypertensive efficacy of telmisartan, administered once daily at doses of 20–160 mg in patients with mild-to-moderate essential hypertension, has been shown to be superior to that of placebo and comparable to that of other common antihypertensive agents. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. The absolute bioavailability of telmisartan is dose-dependent. (1, 2, 3, 4) As per ADR survey, the side effect of amlodipine is higher than the telmisartan. They initially cause edema or swelling, gum hypertrophy, hypotension, etc. The severity of side effect has low not life-threatening condition occurs. As per surveyor's opinion of the physician or patients we had not find the unknown or unreported side effects.

1. INTRODUCTION

Hypertension is considered to be one of the leading causes or factors of increased cardiovascular disease. Hypertension is a very common disorder. It is not a disease itself but it is a very important risk factor for cardiovascular morbidity and mortality. A small number of patients have an underlying renal or adrenal disease as the cause for their increasing blood pressure. Lowering BP does not reduce cardiovascular risks, maintaining systolic BP of less than 125-130 mmHg its prevents complications in patients with diabetes, heart failure, coronary artery disease, stroke, and other cardiovascular diseases. This can be required the guideline for selecting the appropriate antihypertensive medications. However, no clear single identified cause is found and their condition is labeled “essential hypertension”. A number of physiological mechanisms are involved in the maintaining of normal blood pressure. A normal blood pressure range in adults is below 120/80 mmHg. The ‘high normal’ (prehypertension) as 130-139 mmHg systolic and 80-89 mmHg diastolic pressure.

It will be defined as the blood pressure above 139 mmHg systolic or above 89 mmHg diastolic on several reasons or occasions called hypertension.

1.2 Etiology

Obesity, insulin resistance, high alcohol intake, high salt intake, sedentary lifestyle, stress, low potassium intake, low calcium intake, etc. (1, 2)

1.3 Classification of hypertension

Primary or essential hypertension (Cause is known)

Secondary hypertension (Secondary to renal, endocrine and vascular causes)

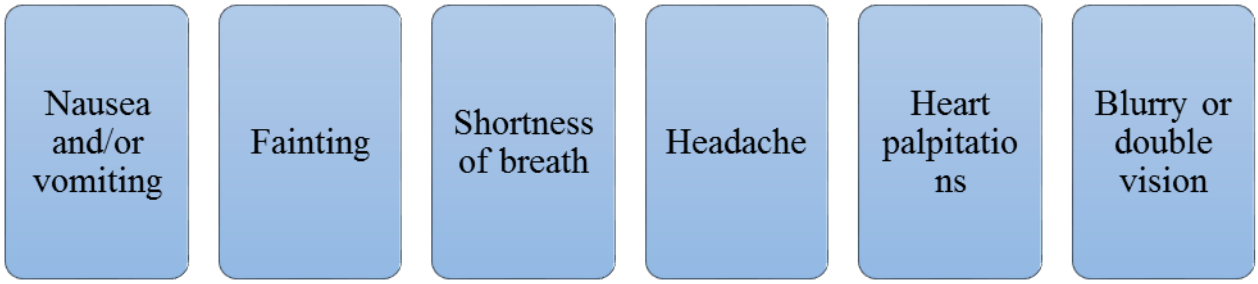
The kidney plays an important role in determining the BP level by doing so via **RAAS,** which has controls both vasoconstriction and volume, the major determinates of BP and tissue flow. Physiologically BP is a product of cardiac output and peripheral resistance (PVR). The BP is controlled by two main types of systems. (1, 2, 3)

The adrenergic nervous system: Which operates through the baroreceptors and is mainly responsible for contracting the acute changes in the BP.

The humoral rennin-angiotensin-aldosterone system (RAAS): In which slow response, is important in the long-term regulation of BP and operates through the kidneys.

Renin cleaves the serum globulin **angiotensinogen** to an inactive decapeptide, "angiotensin I". During its passage through the lungs, is converted into an active octapeptide, "angiotensin II" by the action of **angiotensin-converting enzyme** (ACE). (1, 2)

1.4 Sign and Symptom's



1.5 Antihypertensive activity

Classifications of antihypertensive agents

There are multiple classes of antihypertensive medications or drug therapies used for the treatment of hypertension, following classes are included in first-line treatment,

Thiazide type diuretics

Calcium channel blockers

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)

Combination therapy including above categories.

For antihypertensive activity calcium channel blocker (CCB) plays an important role to control increasing blood pressure. Amlodipine having higher antihypertensive activity as compared to other CCB. As well as angiotensin I receptor blockers (ARB) can also lower the event of cardiovascular dysfunction. In that ARB the telmisartan gives better ARB activity. ARBs inhibitors decrease blood pressure by inhibiting to the angiotensin-converting enzyme.

(1, 2, 3)

Therefore, current guidelines recommend combinations of antihypertensive drugs. Four different classes of antihypertensive drugs are recommended as first-line therapy for

hypertension calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs), and thiazide-type diuretics. (17)

Table.1

	Dosage	**$T_{1/2}$ life**	**Bioavailability**	**Dosage schedule**	**Chemical class**	**Adverse effect**
Telmisartan	20-40mg	20-24hrs	40-60 % (oral)	BD	Benzimidazole	Peripheral edema, heart failure, pulmonary edema, flushing,etc
Amlodipine	2-10mg	30-35hrs	40-70 % (oral)	OD	Dihydropyridine	Palpitation

2. METHODS

Drug ADR Survey:

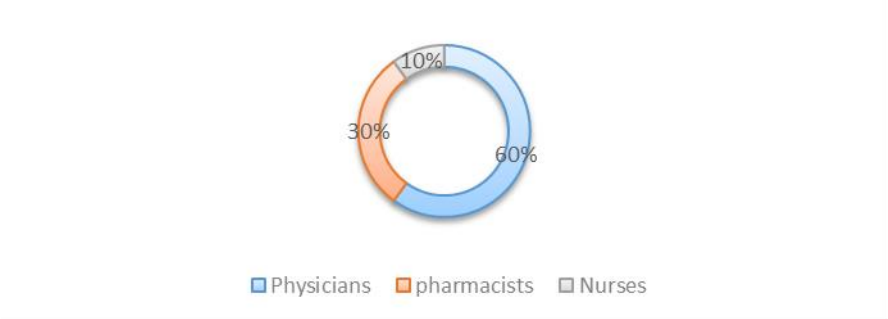
Table 2

Naranjo Adverse Drug Reaction Probability Scale (24)				
	Yes	**No**	**Don't Know**	**Score**
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
TOTAL SCORE				

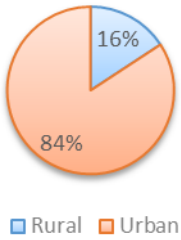
During the survey, we can prepare a questionnaire for healthcare professionals i.e. physicians, nurses, pharmacists also for patients as per the IPC suspected ADR form.

The questionnaire consisted of questions related to, knowledge, availability of reporting system, socio-demographic factors, institutional factors and ADR reporting practice. The questionnaire is as follows;

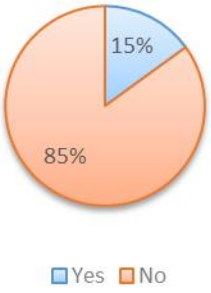
1. Which healthcare professional group do you belong to?



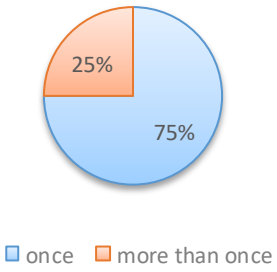
2. Where is your practice located?



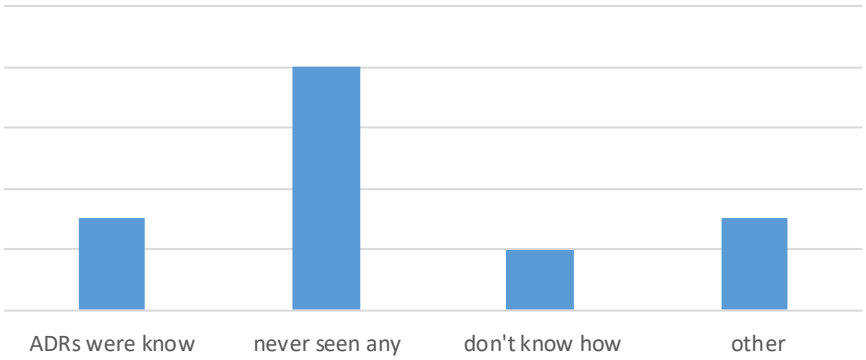
3. Have you reported an ADR before?



4. How many times have you reported?



5. Is there any particular reason why you have never reported an ADR?



6. Do you observe unknown ADR of Amlodipine and telmisartan?

7. How was the severity level seen?

8. Do you noted the same result of amlodipine and telmisartan after two years of chronic use?

9. Derivative replacement is necessary after chronic use please give me your opinion.

10. When the reaction was started?

11. The reaction was stopped after discontinued.

3. RESULT AND DISCUSSION

Initially, we started this project study with the help of research papers, articles, case studies, books, and pharmacopeia. In that we find out the general information of amlodipine and telmisartan like their drug profile, pharmacokinetics, pharmacodynamics, mode of action, excretion, metabolisms, drug interactions, etc. Then we do the market survey or ADR survey of amlodipine and telmisartan. During the survey, we found some limited side effects like

gum hypertrophy, peripheral edema, simple swelling, sudden hypotension etc. During the survey, we can prepare a questionnaire for healthcare professionals i.e physicians, nurses, pharmacists also for patients as per the IPC suspected ADR form. Then we observed Amlodipine and telmisartan on the Naranjo scale. As per the score of Naranjo scale was found to be 6. As per the result interpretation of the Naranjo scale the score between 5 to 8 shows probable ADR.

NARANJO ADVERSE DRUG REACTION PROBABILITY SCALE

The Naranjo ADR Probability Scale was developed to help standardize the assessment of causality for all adverse drug reactions. The scale was also designed for use in controlled trials and registration studies of new medications, rather than in routine clinical practice.

Score 6

Based on the following parameters:

1. Are there previous conclusive reports on this reaction?

Yes +1

2. Did adverse events appear after the suspected drug was given?

Yes +2

3. Did the adverse reaction improve when the drug was discontinued or a specific?

Antagonist was given?

Yes +1

4. Did the adverse reaction appear when the drug was readministered?

Not known or not done

5. Are there alternative causes that could have caused the reaction?

Not known or not done

6. Did the reaction reappear when a placebo was given?

Not known or not done

7. Was the drug detected in any body fluid in toxic concentrations?

Not known or not done

8. Was the reaction more severe when the dose was increased, or less severe when?

The dose was decreased?

Yes +1

9. Did the patient have a similar reaction to the same or similar drugs in any previous

Exposure?

Not known or not done

10. Was the adverse event confirmed by any objective evidence?

Yes +1

Result Interpretation

Range of Naranjo scale -4 to +13

Doubtful ADR (<2): The reaction was likely related to factors other than a drug).

Possible ADR (2 to 4): The reaction followed a temporal sequence after a drug, possibly following a recognized pattern to the suspected drug and could be explained by characteristics of the patient's disease.

Probable ADR (5 to 8): The reaction followed a reasonable temporal sequence after a drug, followed a recognized response to the suspected drug, was confirmed by withdrawal but not by exposure to the drug, and could not be reasonably explained by the known characteristics of the patient's clinical state.

Definite ADR (≥9): The reaction followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, followed a recognized response to the suspected drug and was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.

Probable ADR (5 to 8): The reaction followed a reasonable temporal sequence after a drug, followed a recognized response to the suspected drug, was confirmed by withdrawal but not

by exposure to the drug, and could not be reasonably explained by the known characteristics of the patient's clinical state.

Our study shows a healthcare professionals are quite active in reporting ADR, but some of them are not so familiar with the process. Our study identified only a few healthcare professionals are reported ADR before, majority of healthcare professionals had unfavorable attitudes towards ADR reporting practice and they do not have knowledge on ADR reporting practice.

Our study shows only 18% of healthcare professionals face ADR cases during their professional career. For antihypertensive activity calcium channel blocker (CCB) plays an important role to control increasing blood pressure. Amlodipine has higher antihypertensive activity as compared to other CCB. As well as angiotensin I receptor blockers (ARB) can also lowering the event of cardiovascular dysfunction. In that ARB the telmisartan gives better ARB activity. ARBs inhibitors decrease the blood pressure by inhibiting to the angiotensin-converting enzyme.

As per ADR survey, the side effect of amlodipine is higher than the of telmisartan. They initially causes edema or swelling, gum hypertrophy, hypotension etc. The severity of side effects is low not life-threatening condition occurs.

As per survey or opinion of physician or patients, we has not found the unknown or unreported side effect.

4. CONCLUSION

As per ADR survey, the side effect of amlodipine is higher than the telmisartan. They initially causes edema or swelling, gum hypertrophy, hypotension etc. The severity of side effect has low not life-threatening condition occurs.

As per survey or opinion of physician or patients, we have not found the unknown or unreported side effect.

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