Research Article

AWARENESS AND REPORTING OF ADR OF LOSARTAN: A REVIEW

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A R T I C L E   I N F O

A B S T R A C T

Hypertension is now a day very common disorder particularly past middle age, high prevalence involving both sexes. Compared to normotensives, individuals with a high blood pressure stand a much greater chance of having a stroke, coronary heart disease, heart or renal failure and peripheral artery disease with a substantially higher risk of developing arterial fibrillation and deterioration of cognitive function. So treating hypertension in effective manner with reduced adverse events is a challenge. Various antihypertensives are used e.g. diuretics, beta blockers, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers etc. Our survey focused on angiotensin receptor blocker antihypertensive. Losartan is angiotensin II receptor blocker antihypertensive agent with multiple therapeutic applications such as being used in diabetic nephropathy, left ventricular enlargement, used to reduce risk of stroke and most importantly highest protein binding with minimal adverse reactions. Hospital based adverse drug reactions are monitored to identify and quantify the risk associated with the use of drugs provided in hospital. ADR is also helpful in minimizing preventable ADR and mamnagement of ADR. Our survey focused on to study any severe adverse drug reactions of Losartan and understand its safety. ADR were studied by doing survey of losartan administered by healthcare professionals. Survey was questionnaire based as described in ICH ADR form and Naranjo Algorithm ADR probability scale. Our survey interpretes that losartan found to have probable ADR as per Naranjo Algorithm ADR probability scale indicating Losartan relaxes blood vessels and increases supply of blood and oxygen to heart and exhibits temporal relationship.

INTRODUCTION

Definition

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long term medical condition in which the blood pressure in the arteries is persistently elevated. [1]

Hypertension (HT) is a very common disorder, particularly past middle age. 'Hypertension' couldbe that level of BP at or above which long-term antihypertensive treatment will reduce cardiovascular mortality. The cut-off level to be 140 mm Hg systolic and 90 mm Hg diastolic. Majority of cases are of essential (primary) hypertension, i.e. the cause is not known, like Sympathetic and renin-angiotensin systems (RAS). [2]

Hypertension is by far the most common disease that affects beings, its high prevalence involvingboth sexes and extending to either industrialize and developing countries. Compared with normotensives, individuals with a high blood pressure stand a much greater chance of having during their life a stroke, coronary heart disease, heart or renal failure, and peripheral artery disease, with a substantially higher risk also

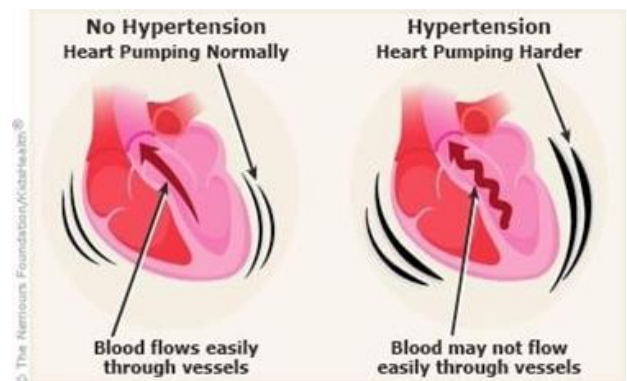of developing arterial fibrillation, deterioration of cognitive function, and dementia. [3]

Fig 1 Hypertension

It is estimated that at least 30% of the adult population in the United States has hypertension, defined as a systolic blood pressure (SBP) greater than 140 mm Hg, a diastolic blood pressure (DBP) greater than 90 mm Hg, or anyone taking antihypertensive medication. Patients at times present to the

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clinic with a severely increased blood pressure (BP), known as a hypertensive crisis [4.]

Types of Hypertension

Primary Hypertension

Primary hypertension is also called "essential hypertension" In most of the cases the causes of this type is not known majority of people with this type feel no different from those who have normal blood pressure. This type of hypertension is diagnosed after a doctor notices that your blood pressure is high on three or more visits and eliminates all other causes of hypertension. Usually people with primary hypertension have no symptoms, but you may experience frequent headaches, tiredness, dizziness, or nose bleeds. Although the cause is unknown, researchers do know that obesity; smoking, alcohol, diet, and heredity all play a role in primary or essential hypertension [5]

Secondary Hypertension

This is when high blood pressure is as a result of other medical problems (like kidney or liver problem) or medication the most common cause of secondary hypertension is an abnormality in the arteries supplying blood to the kidneys. Other causes include airway obstruction during sleep, diseases and tumors of the adrenal glands, hormone abnormalities, thyroid disease, and too much salt or alcohol in the diet. Drugs can cause secondary hypertension, including over-the-counter

Medications such as ibuprofen (Motrin, Advil, and others) and pseudoephedrine (Afrin, Sudafed, and others). The good news is that if the cause is found, hypertension can often be controlled. [6]

Etiology

Most patients who present with hypertensive crisis usually have a history of hypertension. The following list includes some of the commonly suggested causes of hypertensive crisis:

Pregnancy Preeclampsia, eclampsia Medications Compliance sudden withdrawal of medications, especially b-blockers, clonidine. Therapeutic inertia: providers' failure to increase therapy when treatment goals are unmet Drug interactions. [7]

Symptoms

Most people with high blood pressure have no symptoms, even if blood pressure readings reach dangerously high levels. You can have high blood pressure for years without any symptoms. A few people with high blood pressure may have:
Headaches
Shortness of breath
Nosebleeds
Headaches
Bleeding from nose
Fatigue and exhaustionProblem in vision Eczema
Uncertain heartbeatsBloody urine Breathing issue Cold sweating Sleeping problems

Causes of Hypertension

In todays lifestyle risk factors for hypertension are age, poor diet, high sodium content in diet food habits like fatty foods, tobacco and alcohol use, being overweight, lack of exercise, stress etc. These factors may further lead to coronary heart disease, strokes, heart attacks etc if not treated in time.

Complications of hypertension then results in diabetes and kidney diseases. So treating hypertension at initial stages is must to keep heart in good condition and stay healthy.

Treatment of Hypertension

Hypertension can be managed or controlled by making changes to lifestyle such as eating healthy diet regular exercise, saying no to alcohol etc and intake of antihypertensives upon detection of high blood pressure. Different types of medications used for treatment of hypertension are diuretics, B blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers. Regular medications and monitoring the course therapy will help in maintaining blood pressure levels to normal .

Losartan

Losartan is used to treat hypertension and to help protect the kidneys from damage due to diabetes. It is also used to treat lower the risk of strokes in patients with high blood pressure and an enlarged heart. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Losartan belongs to a class of drugs called angiotensin receptor blockers (ARBs). Onset of action of losartan is 3-6 week. It works by relaxing blood vessels so that blood can flow more easily. Losartan reversibly and competitively prevents angiotensin II binding to the AT_1 receptor in tissues like vascular smooth muscle and the adrenal gland. Losartan's prevention of angiotensin II binding causes vascular smooth muscle relaxation, lowering blood pressure. Angiotensin II would otherwise bind to the AT_1 receptor and induce vasoconstriction, raising blood pressure Losartan is available as losartan potassium oral tablets as well as a combination tablet of losartan potassium and hydrochlorothiazide. Patients taking losartan should have their renal function and potassium levels monitored. Losartan was granted FDA approval on 14 April 1995. [8]

Adverse Drug Reactions

Response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function is termed as adverse reaction. ADR are most commonly caused by analgesics and narcotics, antibiotics, cardiovascular agents, anticoagulants, and psycho therapeutics. ADR occur in 1-15% of all drug administrations, but are rarely fatal.

They can be divided into type

1. Dose-dependent or predictable: When any drug is administered in sufficiently high dose, many individuals will experience a dose-dependent drug reaction. For example, if a person being treated for high blood pressure accidentally takes a drug dose several fold higher than prescribed, this person will probably experience low blood pressure (hypotension), which could result in light-headedness and fainting.
2. Idiosyncratic or allergic reactions: Dose-independent adverse reactions are less common than dose-dependent ones. They are generally caused by allergic reactions to the drug or in some cases to other ingredients present in the dosage form. They occur in patients who were sensitized by a previous exposure to the drug or to another chemical with cross-antigenicity to the drug.

Dose-independent adverse reactions can range from mild rhinitis or dermatitis to life-threatening respiratory difficulties, blood abnormalities, or liver dysfunction.

Naranjo algorithm Scale[9]: The Naranjo algorithm Scale or Naranjo Nomogram is a questionnaire designed by Naranjo *et al.* for determining the likelihood of whether an ADR (*adverse drug reaction*) is actually due to the *drug* rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible or doubtful. Values obtained from this algorithm are often used in peer reviews to verify the validity of conclusions regarding adverse drug reactions.

Methodology[9-12]

The study design was observational and survey was done in order to raise awareness of ADR related to Losartan. Survey was conducted for 3-4 months as drug exhibits temporal relationship. This survey methodology involved healthcare professionals (physicians, pharmacists, nurses etc). Survey was done at two levels in first we studied wheather the health care professionals were aware about reporting ADR and second level involved Naranjo Algorithm probability scale based ADR survey of Losartan. Both the levels involved questionnaire. Questions for healthcare professionals were as per the IPC suspected ADR form. It constited of questions related to knowledge, availability of reprting system, socio-demographic factors, ADR reporting practice. For Naranjo Algorithm probability scale based survey of Losartan, questions asked were from Naranjo Algorithm ADR probability scale and ICH ADR form. Form included details of patients and side effects or adverse reactions found in patients after administering Losartan tablets. We had one to one communication with patients and healthcare professionals. Questions asked to healthcare professionals and questions for Losartan ADR are to enlisted below table1:

Table 1 Questionnaire for healthcare professionals and for Losartan ADR

S.N.	Questionnaire for healthcare professionals	Questionnaire for Losartan ADR
1	What healthcare professional group do you belong to?	Are there previous coclusive reports of this reaction?
2	Where is your practice located?	Did the adverse event appear after the drug was given?
3	Have you reported ADR before?	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?
4	How many times you reported ADR?	Did the adverse reaction reappeare upon readministering the drug?
5	Is there any particular reason why you have never reported ADR?	Were there other possible causes for the reaction?
6	Do you observe unknown ADR of Losartan ?	Did the adverse reaction reappeare upon readministering the placebo?
7	How was the sevearity level seen?	Was the drug detected in blood or other fluid in toxic concentration?
8	Do you noted the same result of Losartan after two years of chronic use?	Was the reaction worsened upon increasing the dose? Or was the reaction lessoned upon decreasing the dose?
9	Derivative replacement is necessary after chronic use?	Did the patient have a similar reaction to the drug or related agent in the past?
10	Does the adverse reaction stops after discontinuation of drug?	Was the adverse event confirmed by any other objective evidence?

RESULT AND DISCUSSION

Healthcare professionls like physicians, pharmacists, nurses were part of this survey design proportion of professionals was as shown in fig. 2. Majorly physicians and pharmacists were the focused group and then nurses were questioned.
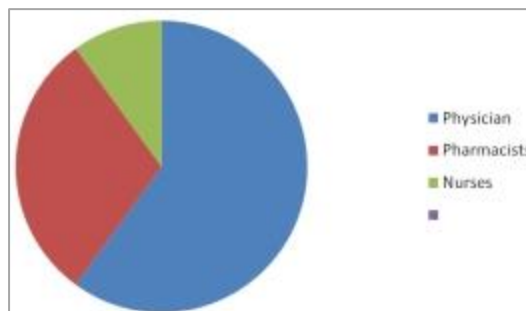

Figure 2

ADR awareness of healthcare professionals from both urban and rural sector were observed as can be seen from fig. 3.
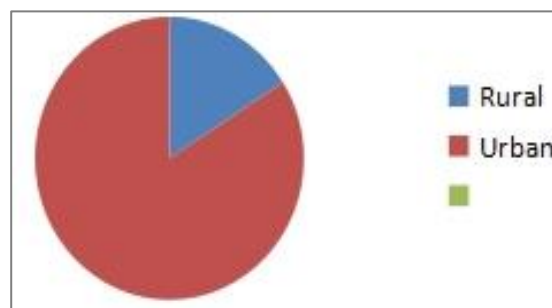

Figure 3

For ADR reporting healthcare professionals were having knowledge about precautionary measures, first aid measures, side effects and how to treat them. In case of any adverse or severe event what has to be done, when to withdraw the medicines or alter the therapy or any combination of therapy is needed or whether to stop the medications all this information was in the knowledge of major professionals except few fellows. So as per survey, professionals were found to have knowledge about ADR but the % of reporting was little bit less where as some were unaware of ADR reporting as shown in fig 4. [13]
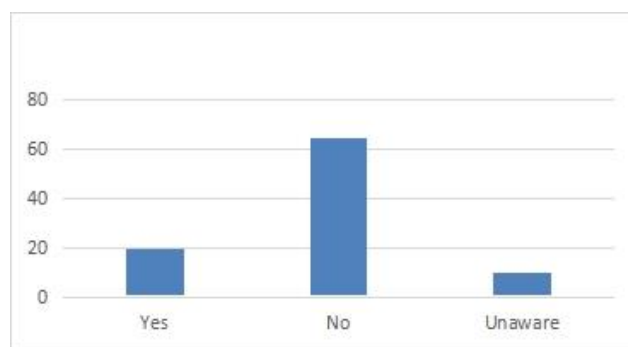

Figure 4

From the above findings reporting of ADR was less and also frequency was around 20%. In case of Losartan they came across events such as headache, nausea, swelling of gum etc .but these were not life threatening. Persistent intake of Losartan was prescribed to patients, Losartan found to shows same type of action but it was monitored for severe events such as shortness of breath and raised potassium levels. Also

as per healthcare professional opinion Losartan was administered alone as well as in combination with other antihypertensive and it can be replaced with other sartans or antihypertensive e.g. Amlodipine if required.

The Naranjo Algorithm ADR probability scale is a method to assess whether there is a casual relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores. Total score ranges from –4 to +13. Losartan is preferable antihypertensive by physicians as it lowers blood pressure and slows down the worsening of kidney problems in diabetic patients.[13] The common side effects associated with Losartan are dry cough (as related to ACE), Headache, nausea and vomiting. Other side effects include muscle pain and joint ache. But common serious adverse effect is hyperkalemia. According to survey patients showed heart palpitations, chest pain, nausea, vomiting, shortness of breath this might have been happened because of raised potassium levels which can be concluded as hyperkalemia. Also our survey found dry cough and diarrhea as conclusive adverse reaction. Reported adverse reactions were seen after the onset of action of Losartan. These adverse events were reversed when Losartan was discontinued. Losartan has a dose from 25mg -100mg and maximum protein binding but no toxicity was reported. Patients were administered a required dose so exact data on increase or decrease in concentration was not established and any objective evidence was not seen. So as per Naranjo Algorithm ADR probability scale ADR score in present survey lies between 5-8 indicating losartan has probable ADR followed by a reasonable temporal sequence after drug administration, it followed a recognized response to losartan, ADR was confirmed by withdrawal but not by exposure to the drug and could not be reasonably explained by known characteristics of patients clinical state.[14] Survey further interprets that severity of side effects of Losartan is low and not life threatening in any of the patients. The Naranjo Algorithm ADR probability scale ADR score of the Losartan survey is as given in following table2:

Table 2 The Naranjo Algorithm ADR probability scale ADR score of the Losartan survey[15]

S.N.	Question	Yes	No	Do Not Know	Score
1	Are there previous conclusive reports of this reaction?	Yes	-		+1
2	Did the adverse event appear after the 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 re appear upon re administering the drug?	Yes	-		+2
5	Were there other possible causes for the reaction?	-	-	Do Not Know	
6	Did the adverse reaction reappear upon re-administering the placebo?	-	-	Do Not Know	
7	Was the drug detected in blood or other fluid in toxic concentration?	-	No		0
8	Was the reaction worsened upon increasing this dose? Or was the reaction lessoned upon decreasing the dose	-	-	Incoclusive	0
9	Did the patient have a similar reaction to the drug or related agent in the past?	-	-	Do Not Know	-
10	Was the adverse event confirmed by any other objective evidence?	-	NO	-	-
				Total Score	6

CONCLUSION

1. Our survey interprets that the healthcare professionals such as physicians, pharmacists, nurses were aware of side effects and adverse events. They were quite active

in reporting ADR but as per our study only 20% healthcare professionals face ADR reporting followed by a recognized response to suspected drug.

2. Our Survey, based on Naranjo Algorithm probability scale concludes that Losartan has probable ADR followed by a reasonable temporal sequence after drug administration, it followed a recognized response to Losartan, and ADR was confirmed by withdrawal but not by exposure to the drug Losartan which was administered orally. Thus as per observation Losartan helps in relaxation of blood vessels and increases the supply of blood and oxygen to heart. Losartan is effective in treatment of diabetic nephropathy in patients with type II diabetes and a history of hypertension acting as protective to kidneys.

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