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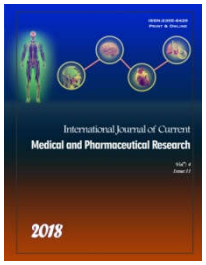

SAFETY OF A DRUG BEYOND MOLECULE: WHAT WE HAVE LEARNED FROM RECALL OF VALSARTAN

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ABSTRACT

Valsartan was a world's number one selling high blood pressure drug .The patents for valsartan and valsartan/hydrochlorothiazide expired in September 2012. The drug is a very good target for the generic industries after patent expiry. However, in July 2018 Drug was recalled due to impurities by various countries including USA and Europe. This recall was due to an impurity, N-nitrosodimethylamine (NDMA), which was found in the recalled products. Later on during review another compound N-nitrosodiethylamine (NDEA) discovered in losartan. NDMA, NDEA are classified as a probable human carcinogen (a substance that could cause cancer) based on results from laboratory tests. The presence of NDMA, NDEA was unexpected still evaluated how they present in drugs.

Earlier most of time pharmacovigilance based the nature of the molecule however this ban also widened our horizon for the impurities that can cause harmful effect. Article discussed in details about the impurities presence and role of physician for drug safety.

INTRODUCTION

In July 2018,the U.S. Food and Drug Administration (USFDA) has alerted health care professionals and patients for a voluntary recall of several drug products containing the active ingredient valsartan, used to treat high blood pressure and heart failure. This recall was due to an impurity, N-nitrosodimethylamine (NDMA), which was found in the recalled products. However, not all products containing valsartan are being recalled. NDMA is classified as a probable human carcinogen (a substance that could cause cancer) based on results from laboratory tests. The presence of NDMA was unexpected and is thought to be related to changes in the way the active substance was manufactured.(1)

Recalling a marketed drug is a very usual phenomenon due to several reasons. USFDA is proactive in this. However, this time scenario is different as after banning 22 countries in Europe USFDA has taken this step(2).

About Valsartan as anti-hypertensive

Valsartan was first developed by Novartis and was sold under the brand name DIOVAN. Diovan (valsartan) was labelled as the world's number one selling high blood pressure medication and accounted for $6 billion in sales in 2010 worldwide. The patents for valsartan and valsartan/hydrochlorothiazide expired in September 2012. The drug is a very good target for the generic industries after patent expiry.

Valsartan is a potent, orally active nonpeptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 which causes reduction in blood pressure and is used in treatment of hypertension. It is a lipophilic drug and possesses moderate onset of action than other drugs of the same category. It is soluble in the neutral pH range. It belongs to the BCS class III drug classified as low permeability and high solubility drug. Valsartan is soluble in acetonitrile and methanol. The drug is rapidly absorbed orally and has limited volume of distribution and is extensively bound to plasma proteins. Valsartan is not extensively metabolized and is mainly excreted by non-renal routes. Valsartan is effective in treatment of paediatric, adolescents and the elderly patients with mild to moderate hypertension. Monotherapy with Valsartan with 80 mg as the starting dose has shown considerable efficacy in patients with CHF and renal impairment along with hypertension and add on therapy helped control BP in large population of patients with severe hypertension not responding sufficiently to β-blockers, ACE inhibitors or diuretics. The importance of aggressive blood pressure control is undisputed, but the therapeutic focus is now extending to end-organ protection as a treatment goal of equal importance to BP reduction. Thus, the value of ARBs like Valsartan in slowing the progression of kidney disease due to

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high blood pressure or diabetes has very positive medical as well as commercial implications. Many clinical trial studies like VALUE, VALIANT, VAL-Heft, PREVAIL and many more have been conducted of which valsartan administration is a part of anti-hypertensive therapy (3)

About Valsartan combination as new emerging therapy in Heart failure

It was known for decades Angiotensin enzyme blocking helps in inhibiting heart remodelling. Various class of Angiotensin converting enzyme inhibitor (ACEI) and Angiotensin receptor blocker (ARB) approved for treatment of Heart failure. Among ARB class Valsartan and Candesartan got special approval for treatment of Heart Failure by Various regulatory agency. It is to be mentioned till few years back there were only handful of drugs in treatment of heart failure with reduced ejection fraction (HFrEF). Blockade of the Renin angiotensin system RAAS was the cornerstone of the treatment of HF.

However, the combination of RAAS blockade with inhibition of neprilysin, an enzyme that degrades natriuretic peptides (NPs), has recently emerged as a potentially superior treatment strategy. In July 2015, the Food and Drug Administration (FDA) approved sacubitril/valsartan (previously known as LCZ696) for use in patients who have chronic and stable but symptomatic HF and who have an LVEF of less than 40%(4) . This therapy gained term as ARNI Angiotensin receptor neprilysin inhibitor got rapid popularity among the cardiologist.

About N-Nitrosodimethylamine (NDMA)

N-Nitrosodimethylamine (NDMA), also known as dimethylnitrosamine (DMN), is a semi-volatile organic chemical, produced as by-product of several industrial processes and present at very low levels in certain foodstuffs, especially those cooked, smoked, or cured. NDMA is water-soluble, yellow in color, and it has little or no taste and odor. It is toxic to the liver and other organs, and is a human carcinogen. It is also used to create cancer in rats for cancer research

N-Nitrosodimethylamine is highly toxic, especially to the liver, and is a known human carcinogen. The US Environmental Protection Agency has determined that the maximum admissible concentration of NDMA in drinking water is 7 ng L−1(5) The US Environmental Protection Agency (EPA) has not yet set a regulatory maximum contaminant level (MCL) for drinking water. At high doses, it is a "potent hepatotoxin that can cause fibrosis of the liver" in rats.(6)The induction of liver tumors in rats after chronic exposure to low doses is well documented(7)Its toxic effects on humans are inferred from animal experiments but not well-established experimentally.

US FDA said that "some levels of the impurity may have been in the valsartan-containing products for as long as 4 years. FDA scientists estimate that if 8,000 people took the highest valsartan dose (320 mg) from the recalled batches daily for the full 4 years, there may be one additional case of cancer over the lifetimes of these 8,000 people(8)

NDMA related impurities in Pharmaceutical products

Over the past few decades' organic chemistry has seen tremendous progress and this has enabled the synthetic chemist to assemble virtually any molecular structure imaginable given reasonable time and sufficient resources. Valsartan is a tetrazole motif and there are several industrial pharmaceutical procedures by which company can generate this compound. In order to generate the tetrazole ring, a nitrile is reacted with an azide, most commonly tributyltin azide(9). Tetrazole derivatives use as medicine as it shows variety of biological activities such as hypotensive), antimicrobial, antiviral, ant allergic, cytostatic, and nootropic among others

There are several procedures to restrict production of other hazardous byproducts while synthesis of this product. Julien Le Roux *et al* showed Cleaning with chloramines is often used to reduce the production of disinfection by-products (DBPs) such as trihalomethanes (THMs) and haloacetic acids (HAAs). This chloramination lead to the formation of N-nitrosamines (NDMA). Among these compounds, the pharmaceutical ranitidine showed the highest molar conversion to NDMA (10)

While review of impurities of valsartan increased there was another impurity detected low levels of impurities N-nitrosodiethylamine (NDEA) in another active substance in Losartan made by Hetero Labs in India. As a result of the detection of this impurity by German authorities now they are analysing these impurities in four sartans namely Candesartan, Irbesartan, losartan and Olmeartan. Both NDEA and NDMA are classified as probable human carcinogen. CHMP currently considers daily intake of 96 ng/d for NDMA and 26.5 ng/d for NDEA associated with this risk level. This would correspond to 0.3 ppm for NDMA and 0.08 ppm for NDEA in valsartan 320 mg tablets. How these impurities came to present in manufacture of sartans yet to be fully established .Like valsartan these active substance have specific ring structure tetrazole(11)

It has been found that source of NDMA contamination in Valsartan Company originated from a Chinese company named Zhejian Huahai Pharmaceutical Manufacturing Active pharmaceutical ingredient (API) of Valsartan. Lot of marketing & formulating company's import API of Valsartan from this Company(12). Zhejiang Huahai has stopped distributing its valsartan API and the FDA is working with the affected companies to reduce or eliminate the valsartan API impurity from future products (1)

On 24th September 2018 FDA has released a gas chromatography-mass spectrometry (GC/MS) headspace method for manufacturers and regulators to detect and quantify NDMA in valsartan API and finished drug products. As per that NDMA impurity should be less than 0.3 ppm.

Current status of Valsartan USA and Europe

This recall applies to three companies: Major Pharmaceuticals, Solco Healthcare and Teva Pharmaceuticals. All the three companies have been asked to withdraw their current valsartan medications from the market. This is a daunting task considering the fact that valsartan is a widespread used drug. (14)

Impact of valsartan recall in India

After the news of contamination of valsartan with NDMA, on July 20, 2018,the Drug Controller General of India has initiated a probe into all companies importing raw material of valsartan from Zhejiang Huahai. The Central Drugs Standard Control Organisation has taken to action and all the imported products are required to be tested before they are taken up for manufacturing. The health care professionals have also been

put on high alert. Novartis, India one of the companies that manufactures the product has initiated recall of specific batches of valsartan that contains NDMA. Despite the initiation of investigation into the issue, no stringent action has been taken to recall drugs containing valsartan in the Indian market. It to be mentioned Valsartan manufactured by two Indian Pharmaceuticals Hetero Pharma and Torrent pharmaceuticals in banned in USA due to impurity.

What needs to be done- Information to prescribers and patients?

- It is advised to the patients taking valsartan to refer the drug name and company name on the label of their prescription bottle. In case of any doubt, patients should contact the pharmacy that dispensed the medicine.
- In the case a patient is taking valsartan product which has been recalled, they should contact the physician or the pharmacist who has dispensed the drug and get it replaced by another alternative drug.
- Patients are advised not to discontinue taking medication on their own, without a doctor's permission. Considering the fact that valsartan is used to treat hypertension which is a serious medical condition, patients taking the recalled valsartan-containing medicines are advised to continue taking their medicine until it has been replaced an alternative drug. As confirmed by the American Heart Association, going off their medication without supervision might be dangerous.
- In case of any suspected ADRs, health care professionals and also patients can report the same to FDA's MedWatch program (12).

Scenario of Drug Safety in India versus the developed world

Over the past two decades, India has emerged as an important clinical trial hub in the world. It is the fourth largest producer of pharmaceuticals in the world. It is now being recognized as the 'Global pharmacy of Generic Drugs' & has distinction of providing generic quality drugs at affordable cost. In a vast country like India, it is important to have a standardized and robust pharmacovigilance and drug safety monitoring programme to protect the population from the potential harm that may be caused by some of these new drugs.

On 14th July 2010,the Ministry of Health and Family Welfare (MoHFW), Government of India launched the nationwide Pharmacovigilance Programme of India (PvPI). As part of PvPI, All India Institutes of Medical Sciences (AIIMS), New Delhi was selected as National Coordinating Centre (NCC) for monitoring ADRs in the country and validating the safety of drugs and medicinal products. 22 ADR monitoring centres (AMCs) were established in the year 2010. The NCC was transferred from AIIMS, New Delhi to Indian Pharmacopoeia Commission (IPC) Ghaziabad on 15th April 2011 for smooth and efficient functioning of program. Selected eligible medical colleges, hospitals and centres were approved as ADR Monitoring Centres (AMCs). Till January 2017, 250 AMCs (government and non-government) have been established under PvPI.

The flow of Adverse Drugs reporting

ADR Monitoring Centres(AMC) are the most peripheral centres responsible for recording the adverse events. These AMCs collect adverse events as per the standard procedure and upload the reports in the Vigiflow software. The Zonal CDSCO centres, situated at Ghaziabad, Mumbai, Kolkata and Chennai,analyze the data and submit consolidated information to the National Coordinating Centre (NCC)via the Vigiflow software and the causality assessments of ADRs are performed utilising the WHO-UMC causality assessment scale system. The zonal CDSCO are under direct supervision of CDSCO headquarters at New Delhi (16, 17, 18).

India's contribution to WHO-UMC's global safety database has reached 3%. The biggest challenges in pharmacovigilance in India are gross under reporting of adverse events. It can be attributed to lack of resources and lack of nation-wide awareness of the concept and importance of pharmacovigilance. The other limitations include non-existent regulatory inspections, wide time interval between guidelines and laws, conservative infrastructure.

CONCLUSION

Apart from active ingredient many inactive substances are mixed with a tablet or capsule. Physician need to report such adverse events if he /she counter to drug to Pharmacovigilance department. They should also up-to-date about the international information and should bring to notice of regulatory. Safety of patient is utmost important and Physician should lead that with proper reporting.

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