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Review Article

REVIEW ON PHARMACOVIGILANCE STUDY OF TELMISARTAN IN HYPERTENSION PATEINTS

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Abstract:

Hypertension is a chronic condition in which blood pressure is higher than normal range. For treatment of hypertension, a broad range of antihypertensive medications are currently available; choice depending upon whether cheaper ones would be equally effective or may have negative impacts on national healthcare budgets. This review covers the Pharmacovigilance aspect of anti-hypertensive drug Telmisartan. Telmisartan is an angiotensin II receptor antagonist used in the management of hypertension. It is highly tolerable than other antihypertensive drugs, but being a xenobiotic has some adverse drug reactions associated with it. Some common adverse drug reactions are headache, upper respiratory tract infection, dizziness, pain, back pain, fatigue etc. Adverse drug reaction means all the noxious and unintended responses that occur after the administration of the drug at any dose in patients which may be related to the drug. The science and systems used for systematically identifying and correlating drugs and side-effects and taking corrective actions fall under the discipline of Pharmacovigilance.

Keywords: Hypertension, Pharmacovigilance, Adverse Drug Reactions, Telmisartan.

INTRODUCTION

Hypertension is a chronic medical condition where the systolic blood pressure is more than 140 mmHg and the diastolic blood pressure is more than 90 mm Hg.1,2 According to the third National Health and Nutrition Examination Survey (NHANES III), approximately 60% of the 50 million Americans with hypertension are at increased risk for cardiovascular disease resulting from uncontrolled hypertension. This is because only 53% of hypertensive patients are being treated and only 24% have their hypertension under control.[3]

Primary (essential) hypertension is the most common form of hypertension, accounting for 90–95% of all cases of hypertension.[4] Secondary hypertension accounts for approximately 5-10% of all cases of hypertension, with the remaining being primary hypertension. Secondary hypertension has an identifiable cause whereas primary hypertension has no known cause (i.e., idiopathic).[5] For the treatment of hypertension, a broad range of antihypertensive medications is currently available. The choice of the more expensive agents, where cheaper ones would be equally effective, may have negative impacts on national healthcare budgets.[6] Antihypertensive drugs are frequently associated with adverse drug reactions (ADRs) that may limit treatment options and reduce patient adherence, which may hinder blood pressure control. These drugs are believed to cause ADRs or symptoms that make patients feel worse than they did before beginning drug therapy for their "asymptomatic" disease.

Typically, clinical trials for new drugs are of short duration and are conducted in populations that number from a few hundred to several thousand; therefore, the most common dose-related adverse drug reactions are usually detected in the pre-marketing phase. Since most trials exclude the elderly, children, pregnant women, patients with multiple diseases, and those on medications suspected of interaction with the study drug, the study participants may not be representative of the real world where the drug is eventually used.[7] An analysis of 192 randomized drug trials found that the quality and quantity of safety reporting may sometimes be presented erratically or may be missing altogether.[8]

The safety evaluation during clinical drug development is expected to characterize and quantify the safety profile of a drug over a reasonable duration of time consistent with the intended long-term use of the drug. Thus, the duration of drug exposure and its relationship to both time and magnitude of occurrence of adverse events are important considerations in determining the size of the database necessary to achieve such goals.10 The science and systems used for systematically identifying and correlating drugs and side-effects and taking corrective actions fall under the discipline of Pharmacovigilance.[9]

Pharmacovigilance

WHO defines, "Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine related problem".[10] It is the process of identifying and responding to the issues of drug safety through adverse effects.[11]

The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) defines an adverse drug reaction (ADR) as an undesired effect of a medication that increases toxicity, decreases desired therapeutic effect, or both.[12]

Aims of Pharmacovigilance

- Detection of severe and unexpected adverse drug reactions to the established drugs and even the minor ones to newer drugs.[13]
- Identification of the risk factors associated with the development of adverse drug reactions and mechanisms of their causation like Type A, Type B, Type C, etc.[14]
- Quantitative estimation of the risk factors, incidence, and prevalence of adverse drug reactions. Estimation of the pharmacoeconomic data related to ADRs.[15]

Need of Pharmacovigilance system

No degree of care and caution at the pre-clinical and clinical testing stages can guarantee absolute safety, when a drug is marketed and prescribed to large populations across the Country and outside. Because clinical trials involve several thousand patients at most; less common side effects and ADRs were often unknown at the time a drug enters the market. Another important drawback of clinical trials is that they can only report adverse reactions that within the finite duration of the trial. Post marketing Pharmacovigilance uses

tools such as data mining and investigation of case reports to identify the relationships between drugs and ADRs. The drug regulatory agencies have the responsibility of having a well-

established Pharmacovigilance system to monitor adverse reactions of drugs. During the drug development phase and later during the life time of a marketed drug. The search for new drugs takes on greater complexity with increasing knowledge, allowing more sophisticated therapeutic interventions. At the same time there is increasing commercial pressure for the pharmaceutical industry to find 'blockbuster' drugs which will be marketed globally to maximize profit in the shortest possible time. Other changes in the industry--shortened times for drug development and increasing outsourcing of functions--make for an environment where some pre-marketing safety issues may go unnoticed. The increasing challenge to Pharmacovigilance is not only to be able to find early signs of drug problems, but to rapidly determine the true benefits and risks. We may not have adequate systems to prevent unnecessary harm from globally marketed drugs.[16]

Medicines are developed over a period of several years. Efficacy and safety of a new drug generally study on a few thousand carefully selected and followed up trial subjects and patients according to strictly defined criteria. For this reason only very frequent adverse reactions and mainly those depending on the drug's pharmacological properties can be observed during its clinical development.

Once the product has been placed on the market, a much larger, and also often polymorbid population will be exposed, which may lead to a change in the drug's hitherto known safety profile. Adverse drug reactions can then be observed more frequently, including those occurring only sporadically and independently of the pharmacological properties of the substance. These new adverse reactions, should be reported without delay as a contribution to a potentially still incomplete safety profile. If such information is consistently forwarded to the competent authorities hitherto unknown risks can be identified and tackled.[17]

Why is ADR monitoring needed?

Adverse drug reactions have been creating headlines over the last forty years since the thalidomide tragedy. Adverse drug reactions (ADRs) present a serious public health problem that can affect patients, caregivers, pharmaceutical companies, and the health care system as a whole.[18]

In the formal evaluation of the drug by clinical trials, many of the drug issues related to the safety are inadequately studied. In addition, the formal therapeutic trials are conducted in carefully controlled conditions; in highly selected and limited number of patients, so that the exact safety profile of the drug in the real life situations is not known. Moreover, prior to its release, a drug is studied in just 4,000 cases. Therefore, adverse reactions having frequency less than 0.5 to 1% are missed. Children, pregnant women, and elderly are not included in clinical trials for ethical reasons. Therefore, the safety of the drug in these cases remains unknown until its release.[19]

According to a study carried out at a private tertiary care hospital in South India, the incidence of ADRs was found to be 1.8%, out of which 12% of suspected ADRs were severe and 49% ADRs were moderate in severity.[20]

Case processing in Pharmacovigilance

Case processing is not detection of ADR. It's a processing of ADR reports that the company receives from various sources. Once the case is received from any source(Telephone, fax, email, licensing agreement, from the regulators or other companies), it has been assigned to the triage team. It checks the case for 4 valid criteria. If the case is valid it is being evaluated for its seriousness and expectedness criteria. A unique identifying number is assigned to each individual case. Then the case is sent to the safety associate for the data entry. The work of the case processing team starts now. The safety associate enters the case into safety database; perform MedDRA coding and writing narratives of the case. In case of any query he/she asks for follow up information to the reporter. After

the data entry the case is assigned to the QC team, where the QC person checks the work done by Safety associate. The case moves in the workflow to the Medical Reviewer who assess the case for Medical aspects, perform the causality assessment and gives a company comment on each case. Now the case is ready for submission to the regulatory authority. The submission team submits the Case to the regulatory authority according to the local requirement.[21]

Indian Scenario

Monitoring of adverse drug reactions started in India about two decades ago (1982). Under the chairmanship of the Drug Controller of India, five centers were established with the idea of starting a programme nationwide. It consisted of three phases: the first one being monitoring of reactions in the institutes, second one in governmental bodies like CGHS, and the third phase proposed to include general practitioners.21 A multi-institutional pilot study involving 58,194 cases was done in 1987 under the aegis of Indian Council of Medical Research. Its nodal center (National Pharmacovigilance Centre) is located in the Department of Pharmacology, All India Institute of Medical Sciences, New Delhi. It is affiliated to the WHO collaborating Centre for ADR Monitoring, Uppsala, Sweden. The others are located in PGI (Chandigarh), JIPMER (Pondicherry), KGMC (Lucknow), and Seth GS Medical College (Mumbai) – special center. Health professionals working in the field of delivering the health care (both conventional and unconventional) like physicians, dentists, nurses, pharmacists, can report suspected adverse drug reactions by letter, phone, fax, e-mail, or by personal contact with any of the five adverse drug reaction monitoring centers located across the country. In many countries, it is mandatory to report all suspected ADRs that occurred in clinical trials for new drugs to the competent authority.[22]

Telmisartan

Telmisartan is a nonpeptide ATII receptor antagonist that selectively and insurmountably inhibits the angiotensin II AT1 receptor subtype without affecting other receptor systems involved in cardiovascular regulation.[23] Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Plasma aldosterone levels are decreased.[24]

Pharmacological properties

Angiotensin II receptor blockers (ARBs) are highly effective antihypertensive agents and are widely regarded as having tolerability profiles similar to that of placebo.[25] Of the commercially available ARBs, Telmisartan has the longest half-life of about 24 h.[26,27] This suggests that Telmisartan should have a long throughout the once-daily dosing interval. Another feature distinguishing Telmisartan from other ARBs is its high lipophilicity.[28] This enhances tissue penetration, intracellular absorption and bioavailability. The high lipophilicity of Telmisartan, in comparison with losartan, may confer vascular protection as has been demonstrated in an animal model.[29] Another feature that distinguishes Telmisartan from the ARBs candesartan, Cilexetil, losartan, and uncertain is that it is not a prodrug; thus antihypertensive potency is related to the activity of the parent compound.[28]

Efficacy

Most studies are of relatively short duration, with only one long-term study of 1-year duration. There is very little information.

Dosage

The recommended starting dosage of Telmisartan for most people with high blood pressure Telmisartan 40 mg once a day. Based on the blood pressure response and/or Telmisartan side effects, the dosage may be increased or decreased. With each change in dosage, it may take several weeks to see the full effect of Telmisartan on lowering blood pressure. The recommended dosage of Telmisartan for the purpose of reducing the risk of cardiovascular problems (such as heart attacks, strokes, and related deaths) in people at high risk for such problems is 80 mg daily.[30]

Adverse Drug Reactions of Telmisartan

Rare side effects of Telmisartan include:

- Insomnia,
- Impotence,
- Migraine,
- Gas,
- Constipation,
- Dry mouth,
- Depression,
- Middle ear infection,
- Asthma,
- Vision problems,
- Serious breakdown of muscle[31]

Telmisartan has been studied extensively in clinical trials, with thousands of people worldwide having been evaluated. In these studies, side effects are always documented and compared to those that occur in a similar group of people not taking the medicine. Based on these studies, the most common Telmisartan side effects include:

- Headache-1.92,
- Upper respiratory tract infection,
- Dizziness- 5%,
- Pain,
- Back pain,
- Fatigue-3%,
- Diarrhea-3%,
- Sinusitis-4%,
- Influenza like symptoms,
- Dyspepsia,
- Myalgia,
- Coughing,
- Chest pain,
- Urinary tract infection,
- Nausea-2%,
- Pharyngitis and abdominal pain[32-36]

Some clinical study are conducted with combination of amlodipine and Telmisartan their result are reduction in the mean SBP and DBP and the overall incidence of ADRs was 7.69% with headache (1.92%) and vertigo (1.44%), as the commonest side-effect.[37]

CONCLUSION

The survey of literature showed that there is a need of Pharmacovigilance about Telmisartan used for the treatment of hypertension because the duration of clinical trial is limited and using this data we are not hundred percent conclude that drug is safe. Therefore we require the awareness about these ADRs to report regularly to respect Pharmacovigilance centers. So, if more attention is focused on the Pharmacovigilance of the drug it may be possible to report more such ADRs which might be beneficial for treatment of hypertension.

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