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Clinical pharmacokinetics of Azilsartan medoxomil for the treatment of cardiovascular disease: A review

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Abstract.:Hypertension related cardiovascular complications could be amplified by the presence of metabolic co-morbidities. Azilsartan medoxomil is a precise blocker of angiotensin 1 receptor that prevent angiotenin binding, resulting in vasodilation and decrease the effects of aldosterone. Azilsartan is a recently approved angiotensin 1 receptor blocker and appears to be more efficacious in reducing blood pressure than other blockers with a similar safety and tolerability profile. Its very high affinity to and slow dissociation from the angiotensin 1 receptor along with its inverse agonistic properties make it a very good candidate for clinical effects beyond simple blood pressure control, potentially counteracting cardiac hypertrohy and cardiac fibrosis. In drug discovery and the development is to optimize candidate selection for the target therapeutic area and to predict the dose and dosing regime for initial clinical trials with due consern to the requirements for effective treatment in the target therapeutic area these are the main role of preclinical pharmacokinetics. Both the pharmaceutical target and drug disposition like absorption, clearance and distribution of new chemical entities with clear understanding and consideration is required for the type of agent and in sequence for the successful approach.

1. Introduction

Over all worldwide, increased blood pressure report is approximately to cause 8.0 million deaths and it is about 13.2% of the total of all deaths. These accounts for 62 million disability adjusted life years or 3.9% of total disability adjusted life years [1]. For treating hypertension eight classes of medications are used now a days.

Angiotensin converting enzyme inhibitors, diuretics,angiotensin II receptor blockers, alphadrenergi c blockers, direct renin inhibitors central adrenergic inhibitor, calcium-channel blockers, and beta-adrenergic blockers are included in this. Seven agents of the angiotensin II receptor blockers class-candesartan such as eprosartan, irbesartan, losartan, olmesartan, , telmisartan, and valsartan were used till now . Many of these drugs are available in combination with other antihypertensive agents, such as the direct renin inhibitors aliskiren, the calcium-channel blockers amlodipine, and the thiazide diuretic hydro-chlorothiazide. Azilsartan medoxomil is a new addition to the angiotensin II receptor blockers class of antihypertensive agents [2]. Food and Drug Administratio n approval has been recorded in the year of 2011.

Generally looking for this compound is angiotensin II receptor blockers class and the angiotensin II

receptor blockers mechanism of action, selective inhibition of angiotensin II by competitive antagonism of the angiotensin II receptors, has been speculated to reduce adverse effects and possibly enhance clinical efficacy. Angiotensin II receptor blockers displace angiotensin II from the angiotensin I receptor and produce their blood pressure lowering eff ects by antagonizing angiotensinII induced vasoconstriction, aldosterone release,catecholamine releas e, arginine vasopressin release, water intake, and hypertrophic response [3-6].

2. Pharmacology of Azilsartan metoximil

Increased activity of the renin angiotensin aldosterone system played a major role in thedevelopme nt of hypertension and related cardiovascular complications. Angiotensin II is the major effectors hormone of the renin-angiotensin-aldosterone system and exhibits a main role in the regulation of blood pressure, fluid-electrolyte balance and pathophysiology of hypertension. Azilsartan is a particular blocker of angiotensin II type-1 receptors that prevent angiotensin II binding, resulting in vasodilation and decrease the effects of aldosterone, because of this type of receptors in the vascular smooth muscle and the adrenal gland. With respect to other angiotensin receptor blockers, Azilsartan is highly selective for the angiotensin II type-1 receptor and not the Angiotensin II type-2 receptor. Azilsartan medoxomil is a prodrug to subject of its active moiety, at the level of the gastrointestinal tract. Approximately 2 to 3 hr this compound reaches peak plasma concentration through oral administration. Without fasting administration not affect bioavailability approximately 57 %. Mainly excreted by the kidney and clearance of 2.3 mL/min. The elimination half-life is approximately 9 to10 hr, after oral administration with the steady state of plasma concentrati ons was reached within five days .Treatment with Azilsartan is healthy tolerated, with similar overall rate of adverse events as compared to placebo. In particular, it has been reported that treatment withdrawal due to adverse events ranged from 2 to 3% [7-8]. Literature review has been shown the most frequently occurring adverse event in sick persons receiving Azilsartan was diarrheal occurring in approximately 2% of sick person receiving the 80 mg dose in placebo-controlled mono therapy trials, compared with 0.5% of sick persons who received placebo [9-11]. Other adverse events potentially related to treatment with Azilsartan included nausea, asthenia, fatigue, muscle spasm, dizziness and cough. In clinical trials, the most common side effects included headache, dizziness, dyslipidemia and urinary tract infection. Dosage forms that are retained in the stomach would increase its oral bioavailability and efficacy. Therefore sustained-release (SR) products are needed for Azilsartan to prolong its duration of action and to improve sick person compliance.

3. Pharmacokinetic Evaluation:

At present bringing a new drug to introduce in market is approximate to be between $750 million and $1.5 billion. Presently a enormous space among the number of candidate medicine compounds in evaluating ones actually get approved [12-15]. Due to lack of understanding of the relationship between dose-concentration response and unanticipated safety events drugs fail at late stages, because of these two key reasons. specified this type of scenario, it is very crucial condition to have possible tools that help to forecast how a drug will carry out *invivo* and help out in the success of a clinical therapeutic candidate. Pharmacokinetics characterizes of the A (absorption), D (distribution), M (metabolism), and E (elimination) properties of a drug. Though, the reason of Pharmacokinetics is to study the time course of amounts and concentration of drug and its metabolite in the variable tissues in the body, and to put up fit to deduce the data. Pharmacokinetics is interconnected with many disciplines, particularly, biop

harma-ceutics therapeutics and pharmacology. Although most of the foundation of pharmacokinatic was laid in the late fifties and early sixties, it continues to be comparatively young discipline among the health science. The origin of pharmacokinetics can be traced back to the papers published by late thirties. Two of these papers were kinetics of distribution of substances administrated to the body and the extra vascular modes of administration and kinetics of distribution of substances into the body. The knowledge of pharmacokinetics can be used for variety of purposes. These may be clinical in nature, or may be interest from an industrial or formulation stand point. Examples of importance of pharmacokinetics include the following:

i) Estimation of rate of ADME properties of a drug in the body.
ii) Estimation of bioavailability of drug from multi-source products marketed by various manufacture containing the same drug.
iii) Estimation of bioavailability of drug from different formulation of the same drug.
iv) Calculation of appropriate dosage regimen for individuals.
v) To describe the time course of drug in the body and calculate the various pK parameters of the drug.
vi) Principle of desired rate of release is the basis for research in various drug delivery systems, e.g., prodrug, coated dosage forms, etc.

Unwavering from plasma concentration of formulations of sustained release tablets of ten critical pharmacokinetic parameters such as extent of protein binding, clearance,effective concentration range, fraction of the available dose excreted unchanged, extent of availability, blood or plasma concentration ratio, half-life, toxic concentration, volume of distribution, rate of availability, AUC0-∞, C_{max}, T_{max}, T1/2, AUC0-t and elimination rate constant. In general, elimination rate constant was calculated from the slope of the terminal elimination phase of a semi logarithmic plot of concentration versus time, after subjecting it to linear regression analysis it ought indomitable for each new chemical molecule in both test animals. The statutory definitionof pharmacokinetics parameters maximum peak serum concentration that a drug achieves in an exacting test area of the body after the drug has been administrated and previous to the administration of a second dose. Concentration maximum is the parallel of Concentration minimum, which is the Concentration minimum, concentration that a drug achieves after dosing. The related pharmacokinetic parameter time maximum is the time at which the Concentration maximum is observed. After oral administration, the Same subject are used to different properties of various formulations, they could be concentration maximum and time maximum are dependent on the level of the rate of drug absorption and the disposition profile of the drug. Quick fix drug side effects are most likel y near the Concentration maximum, whereas the therapeutic effect of drug with sustained durati on of action usually occurs at concentrations slightly above the C_{min}. Bioavailability is the rou te of administration and its galenic formulation determine the amount of administered dose abso rbed into the circulation.

After administered the drug bioavailability depends on many elements like

i) Decomposition of the drug in the lumen.
ii) Determine the dissolution in the intestinal lumen and it absorption across the intestinal wall depend on Physicochemical properties of the drug and its excipients
iii) Surface and time obtainable for absorption.
iv) pH and perfusion of the small intestine.
v) Hepatic first-pass effect.
vi) Complex chemical reaction in the lumen.

Under these conditions, absorption is characterized by an absorption rate constant and a corresponding absorption half-life [16-20].

Absorption of a lot of drugs does not exactly follow linear kinetics. In few cases, the drug can be absorbed in a constant rate and the same amount of drugs is absorbed during every time interval and mimics constant rate intravenous infusion. For that reason in each succeeding half-life and very less drugs are eliminated.

Clearance and volume of distribution depends on the half life of a drug .The elimination half life is considered to be free of the amount of drug in the body. The actual body contact to drug after administration of a dose of the drug based on the area under the plasma drug concentration time curve reflects, it is expressed in mg*h/L. The dose administered to reaches the systemic circulation corresponds to total amount the fraction. The Area Under Curve is directly proportional to the dose when the drug follows linear kinetics. The Area under Curve is inversely proportional to the clearance of the drug. These two distinct phases in the plasma concentration versus time plot are described in the figure-1($t^{1/2}$) can be estimated from the terminal slope of the plasma concentration time profile [21-24**].**

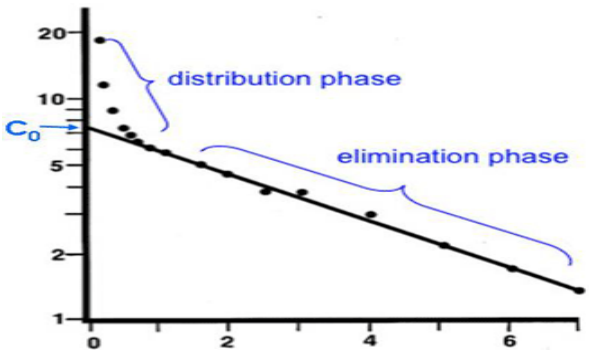

Fig-1. Time course of the plasma concentration of a drug applied by a single intravenous injection

4. Bioavailability Consideration for time release tablets

Mechanism is used in capsules to dissolve gradually and release a drug over time depend upon the sustained-release, sustained-action, extended-release, time release controlled-release, continuous release. The advantages of slow release tablets are frequently being taken less frequently than immediate release formulations of the parallel drugs and they keep steadier levels of the drug in the bloodstream. Most of the slow release drugs are formulated, so that the active ingredient is surrounded in a surrounding substance of insoluble core. Some drugs are covered in the polymer-coated tablets with a laser type drilled hole on one side and on the other side covered with permeable membrane. The porous membrane hard-pressed by the acids in the stomach, potency the drug to come out from surface to surface the laser drilled hole within the time, whole drug releases into the system while the polymer container remains impaired, later on excreted through normal digestion for slow release formulations, the drug dissolves into the matrix and physically swells to form a gel and allowing the drug to exit on the outside surface.

There are certain considerations for the formation of sustained release formulation, if the potent compound has a lengthy half-life; it is stable on its own. Time releasing not related to its blood levels and active compound. If the absorption of the energetic compound involves an active transport, the improvement of releases an active substance gradually, product might be challenging. Finally, if the potent drug was a lesser half-life, it would need a more quantity to preserve a long established efficient dosage. In this particular situation, a huge healing window is required to keep away from toxicity; or else, the risk is needless and dissimilar method of administration would be suggested [25-29].

Bioavailability and bioequivalence studies in new drug approach would be submitted for a not officially accepted, discovered recently drug entity and prodrug derived of a beforehand accepted discovered recently drug entity formulated as a redesigned compound . Also suggested that consequent customized compounds that are pharmaceutically corresponding and bioequivalent to the scheduled drug manufactured goods be submitted as truncated new drug applications. The principle of an in vivo bioavailability investigation for which a controlled-release compounds claim to decide, if all of the subsequent surroundings are met: The active moiety targeted to the slow-release maintain the bioavailability outline well-known for the compound regulations out the incidence of any molecule discarding.

Particular moiety portions and suspension of the active therapeutic moiety depends on the drug product's formulation provides reliable pharmacokinetic performance. A presently marketed, unslow-release moiety, containing therapeutic moiety and administered according to the dosage recommendations in the labelling and slow-release drug product

subject to a permitted occupied new drug application containing the same active moiety component and administered suitably to the dosage suggested in the labelling [30-32].

5.1. *In vivo* bioequivalence Studies for pre-approval and post-approval

5.1.1. Pre-approval and Post-approval

Pre-approval when compounds is in the similar moiety outward appearance, but in a dissimilar potency, and is relation same in its vital and non vital ingredients to the potency of which bioavilability or bioequvalance testing has been conducted, an *in vivo* Bioequvalance demonstration of single or many inferior strengths can be rejected based on dissolution tests and an invivo study on the maximum strength.

Post approval information for immediate release drug moiety approved of *in vitro* and in vivo dissolution by bioequivalence studies, the presence of particular post-approval changes are available in an food and drug administration guidance for industry permitted Scale-Up and Post-Approval Changes-Immediate Release [32].

6.1**. Waivers of *In vivo* bio waivers Studies**

6.1.1. Beaded Capsules - Lesser potency.

Based on the f2 test could be used compare different strength of the compound by variation dissolution method and can be generated dissolution profile for slow release capsules, where they contain active moiety differs only in the number of pellets. Fast bioequivalence study to be carried out only on the maximum strength and an *invivo* studies for lower strengths based on dissolution profiles.

6.1.2. Tablets - Lesser potency.

Lesser quantatiy of slow-release tablets is on the unique dosage form but in a various strength, and almost parallel in its vital and unvital ingredients and it has the same compound release in the system, an *invivo* bioeqivalance fortitude of single or many lower strengths can be excluded based on dissolution profile comparisons, with an *invivo* study only on the more strength.Suggested that the compound exhibit analogous dissolution profiles among the maximum strength and the slight strengths based on the f2 test in at least three different dissolution media : pH 1.2, 4.5 and 6.8. as well as dissolution profile be generated on the test and reference products of all strengths [27] .

7. CONCLUSION

Pharmacokinetics is a further step toward rational and optimal therapy. The aim is to decrease the amount of drug and increase the half-life and preventing danger of toxicity. pK is based on the potential of fraction of the drug absorbed against fraction of the drug-dissolved in different type of formulations. In that slow-release formulations are useful to improve the effectiveness of the compounds strength as well as also improving the cardiovascular disease compatibility, compounds will be got reasonable cost. The dosage form is easy to optimize and very helpful and result in resistance. Azilsartanmedoxomil dose range of 20–320 mg does not require any alteration based on sick person's age, sex, race of hepatic [2].

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