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REVIEW ARTICLE **OPEN ACCESS**

Brief review on Pharmacokinetics and Pharmacodynamics of some biologically important drug molecules

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ABSTRACT
The importance of study of pharmacokinetic and pharmacodynamics of drugs is very must because Pharmacokinetics is the study of what the body reacts with the drug molecules and Pharmacodynamics is the study of what the drug interacts with our body. Approximately 74 percent of medications nowadays are taken orally and are proven to be less effective than expected. Pharmacodynamics is concerned with receptor binding, post-receptor effects, and chemical interactions in drugs. Therefore, in this revies we have tried to study a brief literature on some biomolecules which are getting very much significance in pharmacy some of which are as Alfuzosin, Lamivudine, Ketamine, Phenibut Sitagliptin, Metoprolol and Nebivolol. Now a days all we know that how he drugs molecules are being used as biomolecules in medicinal applications to treat various diseases. Secondly, we also know that the drug molecules must have compulsory uses in various diseases because of we know nowadays peoples cannotgetting good food for eating because farmers are using pesticides in large amount to grow crops in very good quantity and to get more profit.Therefore,it's very much scope to study drug molecules pharmacokinetics and pharmacodynamics.
Keywords : Pharmacokinetics, Pharmacodynamics and PK parameters value, Structure Activity Relationships (SAR) etc.

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INTRODUCTION

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. Pharmacokinetics is a branch of pharmacology dedicated to determining the fate of substances administered to a living organism [1, 2]. Pharmacodynamics means that in terms of a drug effect in relation to its concentration in a biological fluid, usually at the site of drug action. Pharmacokinetics is the motion of a drug through the body's biological systems. In short pharmacodynamics means 'what the drug does to the body. These both the processes include five steps absorption, distribution, bioavailability, metabolism, and elimination(ADBME) [3]. Chemical rings, chains, and functional groups make up most medication molecules. Chemical rings make up a significant part of medication structures. Heterocyclic rings have also been exploited as bio isosteres of metabolically unstable functional groups in specific cases [4]. A drug's chemical structure impacts its physicochemical qualities, as well as its Liberation, absorption, distribution, metabolism, excretion, and toxicity (LADME/Tox) properties, all of which influence the drug's pharmacological activity [3, 5, 6].

One of the important factors to obtain required drug concentration in systemic circulation for intended pharmacological response is solubility, which is the phenomena of solute dissolving in solvent to produce a homogeneous system.[7]Small molecule medications, which are any organic substance with a low molecular weight, have several specific therapeutic advantages because of most medications can be taken orally and pass-through cell membranes to reach intracellular targets, there is a need to research their pharmacokinetics and pharmacodynamics [1,2, 8].

In this review article we have tried to study these two phenomena in case of drug like Alfuzosin, Lamivudine, Ketamine, Phenibut Sitagliptin, Metoprolol and Nebivolol because we have seen these drug molecules becoming very much importance in drug delivery system which is as shown in figure number 1 given below.

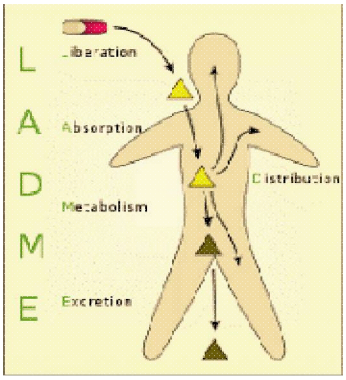

Figure 1 : Representation for ADME Process

STRUCTURE ACTIVITY RELATIONSHIP OF DRUG MOLECULES IN RELATION TO PHARMACOKINETICS AND PHARMACODYNAMICS

The structural–activity relationship (SAR) describes the link between a molecule's chemical structure and its biological activity that means it can be used to predict biological activity from molecular structure [9]. This robust method is used in drug discovery to lead the acquisition or synthesis of desirable novel compounds, as well as to further characterise the existing molecules and it permits modification of the action or potency of a bioactive substance (usually a drug) by modifying its chemical structure [10-12]. As a result, the Structure-Activity Relationship (SAR) is one of the most essential concepts in drug development. SAR reveals precisely which places on a molecule can be modified to improve specific attributes such as solubility, potency [13-15]. QSAR research can be used to develop and identify novel inhibitors, as well as to optimise the absorption, distribution, metabolism, excretion, and toxicity profiles of identified compounds from multiple sources [16-18].

1. **STRUCTURE OF DRUG MOLECULES [19]**

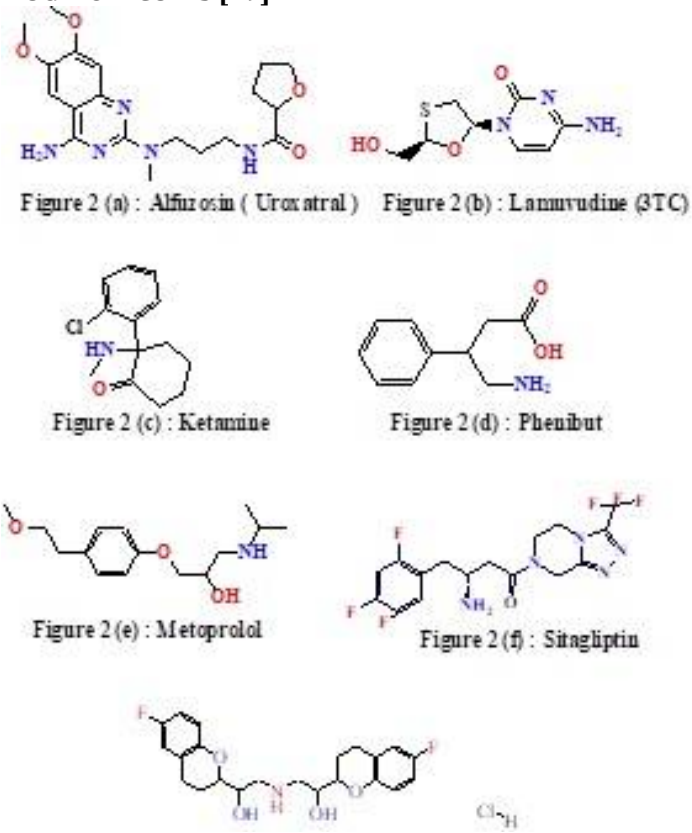

Figure2: Structure of Drug Molecules 2a: Alfuzosin, 2b:Lamivudine, 2c: Ketamine, 2d: Phenibut2e: Metoprolol, 2f: Sitagliptin and 2g:Nebivolol Hydrochloride.

PHARMACOKINETICS AND PHARMACODYNAMICS OF DRUG MOLECULES

ALFUZOSIN

The purpose of this study was to evaluate the pharmacokinetic predictability of alfuzosin, administered orally at doses of 1, 25, and 5 mg to some young healthy individuals [20]. After oral administration, alfuzosin's pharmacokinetics are rapid and well absorbed. After an oral dose of alfuzosin, the mean time to peak serum concentration is 1.5 hours. Within 1.5 hours of taking an oral dose, improved peak and mean urine flow rates were observed. The alpha-adrenergic blocker alfuzosin is used to treat benign prostatic hyperplasia (BPH). It works by relaxing the muscles in the prostate and bladder neck, allowing you to urinate more easily. It takes 3-5 hours for the drug to reach its terminal half-life. In plasma, alfuzosin is 90% protein bound, with 68.2% bound to human serum albumin and 52.5 percent bound to human serum alpha-glycoprotein. Alfuzosin is extensively metabolised by the liver, with only 11% of the administered dose being excreted unchanged in the urine. The parameters obtained from plasma alfuzosin concentrations after administration of the three doses show that pharmacokinetics of alfuzosin is linear in the range of doses 1–5 mg.[20]Three metabolic pathways metabolise alfuzosin: oxidation, O-demethylation, and N-dealkylation. Pharmacologically, the metabolites are inactive [21, 22].

Alfuzosin, a quinazoline derivative is a selective and competitive 1-adrenoceptor antagonist that reduces sympathetically regulated tone of prostatic smooth muscle, alleviating lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). In a binding investigation employing enzymatically separated myocytes from the human prostate and renal arteries, alfuzosin appeared to be more selective for the prostate than tamsulosin, doxazosin, and terazosin. Patients with BPH had greater alfuzosin concentrations in the prostate than in the plasma 12 hours after the final oral dosage. Urinary flow rate increased considerably and dosage-dependently 90 minutes after a single oral dose (2.5mg) and several doses of alfuzosin were given to patients with BPH. Three doses of alfuzosin 2.5 mg three times a day resulted in a considerable reduction in maximum detrusor pressure.[23]

LAMIVUDINE

Intracellular enzymes phosphorylate lamivudinealso called as 3TC to produce lamivudine triphosphate, the putative active metabolite.Lamivudine inhibits HIV-1 and -2 in human PBLs, monocyte/macrophages, and tumour cell lines. In vitro, lamivudine plus zidovudine, didanosine, stavudine, saquinavir, delavirdine, or nevirapine showed synergistic action against HIV-1.PBLs and other cell lines treated to lamivudine showed minimal cytotoxicity [24]. No evidence of reduced DNA synthesis was found in PBLs exposed to the medication [25].

Lamivudine resistance has evolved fast in viral isolates from individuals infected with HIV-1 who have received the medicine as monotherapy (87 percent at 12 weeks) or combination therapy. During lamivudine exposure, the lamivudine resistance mutation antagonised zidovudine resistance and partially restored HIV-1 phenotypic sensitivity. However, lamivudine and zidovudine resistance has been reported in clinical isolates from individuals who received both drugs together [26, 27].

Oral lamivudine is well absorbed and has good bioavailability (mean absolute bioavailability >80% in adults and 68%), while there is substantial interpatient variation in oral absorption. In a dose-ranging study, lamivudine had a mean volume of distribution of 1.3 L/kg. There was a low CSF:serum ratio (0.06) in 6 HIV-infected people. In children, increasing lamivudine oral dosage increased CSF concentrations. Lamivudine appears to freely pass from maternal to foetal circulation across the placenta. Lamivudine is generally removed unaltered by the kidneys. The area under the serum concentration-time curve (AUC) of lamivudine increased 270 and 500 percent in individuals with moderate or severe renal impairment compared to healthy controls. Few data are available on interactions between lamivudine and other drugs [28-30].

KETAMINE

Ketamine metabolism is characterised by a low (10–30%) binding to plasma proteins. Ketamine has a far wider dispersion than thiopental due to its five-fold higher liposolubility [31].

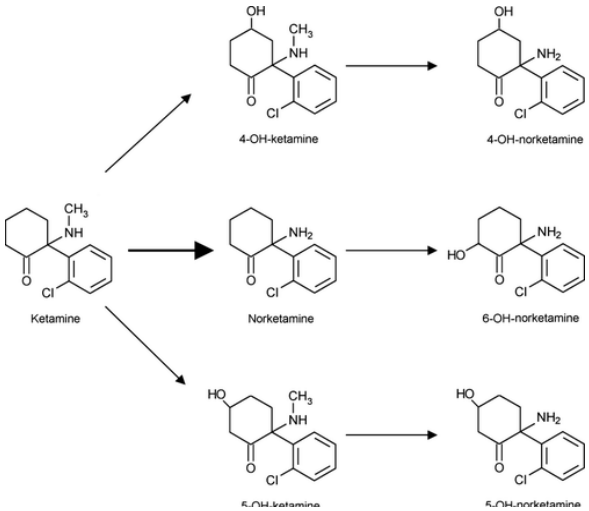

Figure 3 :Metabolism of Ketamine is metabolized mainly to nor ketamine

Ketamine is predominantly metabolised into nor ketamine (80%) by a microsomal enzyme system (N-demethylation), an active metabolite that is then hydroxylized into 6-hydroxy-norketamine (15%) and eventually eliminated in bile and urine after glucuronoconjugation. As illustrated in figure 3 [32], three other less significant metabolites are also produced. Another method converts ketamine to hydroxy ketamine (5%) directly. The liver isn't the only organ involved in metabolism in animals; the kidneys, gut, and lungs all play a role. The half-life of ketamine is 2–3 hours. A tree compartment model can be used to characterise its pharmacokinetics. It's possible that women's clearance is 20% greater than men[33]. In children, intramuscular absorption is faster than in adults. This phenomenon could be linked to children's muscle weakness and regional flow variations. Although the distribution volume is lower (1.9 l/kg), plasma clearance is higher (16.8 ml/kg/min) than in adults. In youngsters, the elimination half-life is also shorter: 100 minutes [32].

PHENIBUT

Phenibut has a structure and pharmacodynamics like baclofen (-(4-chlorophenyl)-GABA). Phenibut withdrawal. However, they needed roughly 10 mg of baclofen per gramme of Phenibut in this case [33]. Phenibut (β-phenyl-γ-aminobutyric acid) is a psychoactive GABA analogue sold online as an anti-anxiety and cognitive enhancer. Its use is expanding; however, its pharmacological activity is similar to that of a prescription sedative. This review will cover the risks of using Phenibut and what therapy alternatives may be beneficial to affected patients.[38]From the recent reports it found that several case studies have emphasised phenibut's propensity to cause physical dependence, withdrawal, and addiction. Intoxicated patients have shown varied degrees of mental abnormalities, from limited responsiveness to frantic delirium [34-36]. Phenibut is a powerful GABAB agonist that is becoming increasingly popular online. Since it can induce physiological changes associated with physical withdrawal and dependence, it cannot be sold as a “dietary supplement” [37.

METOPROLOL

Metoprolol is a well-known 1 adrenoceptor antagonist with no intrinsic sympathomimetic action. It has a less inhibitory impact than propranolol on isoprenaline mediated tachycardia and lowers exercise heart rate than beta -blockers with intrinsic sympathomimetic activity. Metoprolol reduces systolic blood pressure quickly in hypertensive patients, but not diastolic blood pressure. Antihypertensive impact size and long-term haemodynamic alterations are disputed factors. Reduced cardiac effort reduces myocardial oxygen demand, which is significant in ischemic heart disease. Intravenous treatment reduces blood pressure, heart rate, and cardiac output both during rest and during exercise. It reduced ejection fraction in patients with anterior wall hypokinesia but not pindolol. Both medicines shortened hypokinetic segments, but only metoprolol shortened non-hypokinetic segments. Metoprolol's mechanism of action in myocardial infarction is unknown. In some animal trials, metoprolol slows the progression of hypo perfused myocardium to necrosis [38].

It contained 100 mg metoprolol and 12.5 mg hydrochlorothiazide. The pharmacokinetics and pharmacodynamics of metoprolol were compared to a standard combo pill [39]. Despite the controlled-release formulation's lower relative systemic availability (68%) and smaller AUC, metoprolol from the controlled-release formulation had a bigger total effect, measured as the area under the curve of the effect on exercise heart rate vs. time [40]. Both formulations absorbed hydrochlorothiazide quickly, and the plasma concentration profiles were nearly identical. Controlled-release metoprolol with

hydrochlorothiazide provides effective 24-hour 1-adrenoceptor blockage without compromising hydrochlorothiazide pharmacokinetics [41-44].

SITAGLIPTIN

The structure of drug molecule as shown in above figure 2(f) , two randomised, double-blind, placebo-controlled studies with single oral dosages of dipeptidyl peptidase IV inhibitor sitagliptin have been published. Sitagliptin had an apparent terminal half-life of 8 to 14 hours and was well absorbed (almost 80% unchanged in urine). There was little effect on renal clearance of sitagliptin, which was 388 mL/min. The area under the plasma concentration–time curve for sitagliptin rose dose-dependently. Single doses of sitagliptin lowered plasma DPP-IV activity markedly and dose-dependently, with up to 80% suppression at 50 mg or higher for 12 hours and up to 100% for 24 hours. Compared to placebo, sitagliptin doubled post-meal active glucagon-like peptide 1 levels. In addition, it did not produce hypoglycaemia [45, 46]. The proportion of sitagliptin dosage unchanged in urine was largely dose independent and was around 80%. The renal clearance of sitagliptin was also dosage dependant, averaging 388 mL/min [47].

Time profiles for mean plasma DPP-IV inhibition after single oral sitagliptin doses. The % inhibition of plasma DPP-IV enzyme activity increased with sitagliptin dose from 1.5 to 600 mg. At 12 and 24 hours following dosage, sitagliptin was significantly different from placebo in DPP-IV WAI [48, 49]. The pharmacokinetic-pharmacodynamic link between plasma sitagliptin concentrations and DPP-IV inhibition. Individual DPP-IV activity versus time graphs revealed no hysteresis (data not shown), indicating that plasma sitagliptin concentration alone explained inhibition of plasma DPP-IV activity for each patient [50,51,52]. It had no effect on glucose, insulin, glucagon, or C-peptide levels following standardized meals at 4, 10, and 24 hours [53].

NEBIVOLOL HYDROCHLORIDE

Nebivolol is a beta-blocker under FDA assessment for hypertension. Nebivolol has strong selectivity for the β-1 receptor and a nitric oxide-mediated vasodilatory action.[54] Compared to placebo, the medication significantly lowers blood pressure.[54] Blood pressure-lowering effects of nebivolol have been compared to those of other drugs such as atenolol, bisoprolol, amlodipine, and lisinopril. Nebivolol is as tolerable as or better than these agents. The inclusion of nebivolol to the treatment regimen improved the time to all-cause death and cardiovascular hospital admissions in senior patients (70+). If approved, nebivolol could be used to treat hypertension and heart failure, although more research is needed in people with coronary artery disease.[55–57]

DISCUSSION AND CONCLUSION

In this review we have tried to cover the brief review information regarding above mentioned drug molecules for doing feature Ph metrically complexometric research. Therefore, the drug toxicity and adverse drug reactions can be prevented by studying pharmacokinetics, pharmacodynamics and drug interactions in the elderly. Chronic illness increases with age and anatomical and physiological changes impact drug distribution, metabolism, and excretion.

The conclusions of the research that to improve pharmacokinetic and pharmacodynamic models for various drug therapy regimens and interactions. The social and psychological elements of senior pharmaceutical use. Conduct longitudinal studies on older people's medication use. Create research databases linking health outcomes and prescription medicine data and consider a national data repository.

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