International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Volume 1 | Issue 2 | July – Dec- 2017
www.ijpcr.net

Review article *Clinical research*

ISSN: 2521-2206

Pharmacokinetics/pharmackodynamics (PK/PD) model in psychaitry and its relevance intherapeutic drug monitoring (TDM): a review in variability of pharmacotherapeutics

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ABSTRACT

Pharmacokinetic and Pharmacodynamic theory and application has revolutionized the thoughts of neuropsychiatry and the fate of drugs in this complicated system. Neuropsychiatry dugs have done wonders in this decade. On the basis of diverse pharmacokinetic-pharmacodynamic modelling concepts, it has become possible to describe and predict the time course of drug effects under physiological and pathological conditions. The study of pharmacokinetic-pharmacodynamic relationships can be of considerable value in understanding drug action, summarizing extensive data, building a knowledge repository, finding optimal dosage regimen, and in making prediction under new circumstances. Evaluation of PK/PD assumes as a diagnostic tool for under lying disease effects.

Keywords : Pharmacokinetics, Pharmacodynamics, Therapeutic Drug Monitoring, Central Nervous System, Volume of Distribution, Tricyclic Antidepressants, Drug Drug Interactions, Area Under Curve, Cytochrome P- 450

INTRODUCTION

Vast amount of new information on physiology of vasculature has become available but the relevance for clinical practice has not yet been well defined in many instances. The physiology of vascular system is more complex than has been imagined. This not only makes it difficult to integrate available information into coherent whole but also poses a major challenge to the design of therapeutics [1].

For majority pharmacotherapies an important determinant of access of drug to its target site is distribution through systemic compartment whereby drug molecules reach target tissues at a rate determined by blood flow to that particular organ. Being a rate limiting factor, blood flow influences drug transport across vascular

endothelium, to the target sites of action for pharmacological desired or undesired response. [2]

Cellular fractionation and radio-autography studies reveal that most drug molecules are associated with structures having nothing to do with the specific drug effect, thus small fraction of the drug associated with their target receptors is pharmacological representative. [3] Most of the drug molecules will be in the ambient water phase in equilibrium with those bound to its receptors.

In-vitro and *in-vivo* studies show that magnitude of response to a drug is a function of its concentration in the fluid bathing the site(s) of action and hence therapeutic objective can be achieved by maintaining an adequate concentration of drug at that particular site for the stipulated duration of therapy. [4] Simultaneously, the drug distributes to all other tissues including those organs that eliminate it from the body, notably liver and the kidneys. Well calculated dose, adjusted for all probable sources of variability in drug response in a particular patient may prove therapeutic in some patients, ineffective in others and toxic in still others in combination treatments. Adjustments are therefore needed, especially for drugs having narrow therapeutic window, steep concentration-response curve and are used for extended periods of treatments. [4] Step-by-step *PK* of a drug unfolds after its oral administration and further complexities are brought in by administration of concomitant treatments that interfere with the *PK* of initial drug through physiological melio of the body functions. [5] Therefore, for optimal drug administration and monitoring of treatments, knowledge is needed not only of kinetics of drugs but also how kinetics is influenced by resultant change in physiological processes by these drugs.

Response to a single drug is predictable but in case of co-administration of drugs for co-morbid conditions, the concentration of the drug and clinical pharmacological responses are unpredictable. [4] Resulting response may be an expression of pharmacogenetic trait of the individual or of altered physiology leading to alteration in *PK* of the drug disposition. Blood flow rates may differ several folds between rest and exercise. [2] Exercise may influence the rate and extent of kinetics of drugs by changing some of the physiological factors. [6] Circulating minute volume of blood that varies directly with blood pressure and inversely with peripheral resistance may also influence the responce. [2]

Good examples of kinetic consequences of altered blood flow are hard to find, not because they are uncommon but because a number of additional complications always occur concurrently. Thus the kinetic consequences of altered blood flow are examined with the realization that in therapeutic scenario the effects of change in more than one physiological variable needs to be considered. [7] Since blood flow may influence drug absorption, distribution and elimination, it is not surprising that pharmacokinetics of drugs may be altered in circulatory disorders. [2]

Change in one physiological parameter causes change in others, hence drugs remain in dynamic state within biological system and events often happen simultaneously. Pathological conditions make the balance more complex. [8] Pharmacokinetics and pharmacodynamics determine fate of a drug as well as the response characteristics under definite conditions in patients. Application of *PK*/*PD* model makes it possible to understand the quantitative relationships and describes how drugs work by relatively simple concept that can be used to optimize the best outcome of drug therapy. [9] Capillary surface area to volume ratio is considered essential for plasma to tissue equilibrium of circulating drugs. Intravenous nor-adrenaline that induces vasoconstriction and reduces number of capillaries for exchange of a drug is the potential explanation for low concentration of antibiotics in target tissues as studied in critically ill patients. Low MIC values may, therefore, trigger emergence of bacteriological resistance. [10]

Mental health and hypertension are special areas where emphasis is laid on rational therapeutics. Depression and hypertension is a physiological and pathological change due to dysregulation of neurotransmitters in the CNS as well as heamodynamics at the peripheral level. The treatment of these co-morbid conditions needs drugs belonging to different pharmacological classes and receptors [11, 12] Decrease in peripheral resistance by a dihydropyridine arterio-venousdilator (amlodipine), leading to change in blood flow, [13] could produce a window to understand if and how pharmacokinetics could change for amitriptyline, used in this study as a *PK*

outcome marker. Secondly, if treatment for hypertension and co-morbid conditions that may be a cause or consequence of hypertension, would merit a consideration of a possible physiological drug drug interaction even with the two drugs like amitriptyline and amlodipine that are otherwise unreported to have any interactions [14]. The rational of selecting amitriptyline for the study was based on the fact that its tissue and plasma PK has been studied thoroughly and its safety, tolerability and ADRs are well assessed as it has a long history in the clinical practice [15]. Measurement of pharmacological effect of a drug and adjustment of its dose/regimen as a function of effect produced by another concomitantly given drug may be the most appropriate approach in situations where population involved may be significantly sizable for example treatments of patients of hypertension with complications. The relationship detected may have a putative prognostic/diagnostic value in treatment failures or altered pharmacological responses, in such cases.

PK parameters derived are of great usage in dosage adjustments. Volume of distribution (V_d) and clearance (C_L) permit prediction of dose, necessary in a patient to produce a "specific effective concentration level." [(16)] When the *PK* studies are performed the estimated parameters depend on what has been measured, for example metabolites, unbound or total drug. Nevertheless, if the binding is linear in the range of therapeutic or toxic concentrations, the free and total concentration are simple ratios and it is not necessary to measure the free concentration. [17]

Dose predictions are simple applications of the elementary *PK* principles that permit estimating a target concentration from the concentration-effect relationship after administration of a specific dose or regimen. There are two approaches like *PK/PD* and TDM in clinical practice. *PK/PD* is based on the concept of target and its immediate relation to an effect. Biomarker assays help in identifying biological response to a drug candidate [18].

For nonvolatile drugs as adopted in this study, there have been very few instances in which kinetic models of a drug have been linked to cardiovascular pharmacodynamic models. [19] In case of non cardiovascular drugs this approach was developed with a view to link simple cardiovascular *PD* with *PK* model as it has the potential to provide evidence for rational basis to devise regimens and adjustments in drug treatments that allows insight into logistics of controlling any therapeutic failures or side effects due to deviated *PK* as a result of physiological interaction. This model may make it possible to predict systemic consequences of other treatments in patients when dihydropyridine type of antihypertensive drug is prescribed for hypertension arising during course of pre-existing disease. This approach has the potential to provide insight into difficulties that possibly could arise in implementing available knowledge of *PK* for most drugs in therapeutics as blood flow distribution can alter the essential components of drug kinetics. Therefore, the kinetic model of the treatment of a particular disease requires the model to have the physiological basis so as to be able to account for the changes of blood flow on the disposition of the drugs.

When devising model of cardiovascular system, what merits consideration is that a drug with multiple mechanisms of action may produce a broad clinical effect in a heterogeneous population over a relatively narrow concentration range. Hence on the same principle amitriptyline was selected as a surrogate marker in this study in a cardiovascular model to identify changes in its concentration and the concentration of its metabolite nor-triptyline. There is a complex *PD* profile of TCA's. They produce a number of undesired as well as desired effects and are categorized as narrow therapeutic index drugs [20]. The study was purposely carried out using a single optimal dose of a model substrate drug with a low therapeutic index so that any possible increase in its levels after a coprescribed drug will not result in a serious untoward outcome.

"Rational Pharmacotherapy" utilizes the pharmacologic diversity of medication options to advantage in selection of treatments by tailoring treatment of the individual patient based on the specific patient profile, comorbid physical illnesses and concomitant medication. Hence, for rationalization of therapy one needs to anticipate vulnerability of particular mechanisms to change exhibited by some if not all pharmacological agents and the likelihood of significant pharmacokinetic and/ or pharmacodynamic interaction [21]. In the present study attention has been focused on the pharmacokinetic alterations of a drug in selecting the treatment procedures while instituting treatment of hypertension that may happen to exist as a concomitant disease. This provides the rational

basis for sequential use of pharmacological agents if initial benifits are lost and the therapy becomes unsuccessful.

In order to optimize the tolerability and efficacy of antidepressants, one has to take care of the metabolite of the active drug which in itself may be active, in order to bring the synergistic response while treating the psychiatric diseases. There is an inter-individual variability in *PK* and *PD* of TCAs in general even in physically healthy people [22]. In patients dosing becomes complex due to considerable inter-patient variability in *PK*. There exist differences in dose-response relationships for both efficacy and toxicity. This degree of variability is compounded by additional factors such as age and coexistant illness. Under routine dosing conditions patients develop inconsistent plasma concentrations; some develop inappropriately high plasma concentrations and experience additional adverse effects of the medication or some may lose the effect [23].

Tricyclic antidepressant metabolites play an important role in clinical therapy. These drugs undergo extensive biotransformation. The ratio of metabolites to parent drug can be highly variable based on inter-individual differences in rates of biotransformation and elimination. Clinical response may at times be primarily a function of the metabolite. Therefore, to know the pharmacology of antidepressant metabolites, there is need to properly interpret the clinical response in depressive patients. Even hydroxylated metabolites of TCAs inhibit biogenic amine uptake. Their significance arises when it has been seen that in elderly persons and patients with decreased renal function the polar metabolites can accumulate several times in excess of the parent compound [18].

Age, co-morbid medical illness and concomitant medications are certain characteristics for efficacy, tolerability and safety issues in TCA's prescription. These have major impact on the treatment *vs* risk profile and likelihood of a successful outcome and can guide the clinician through a matrix of patient variables along with PK and PD variables [18].

Tricyclic Antidepressants

Need for chronic use drugs with small therapeutic index, large inter individual variability in the dose-plasma level relationship, difficult detection of early toxicity, long delays in onset of action and well-defined concentration-response relationship like TCAs guarantee routine monitoring in patients by a well established TDM programme because same dose of TCA in physically healthy individuals have 30 times variability in plasma levels. The strongest of these plasma concentration-response relationships have been demonstrated for amitriptyline, nortriptyline, desipramine and imipramine. It has been observed that TCAs administered on dose titeration basis only, will generally produce a response rate (i.e, at least a 50% drop in depressive symptom severity) of 60-70% and a remission rate of 30-40%. When the dose is adjusted on plasma drug level monitoring, TCAs remission rates increase from 42% for imipramine to 70% for nortriptyline. [24] Depression is a chronic condition that is more prevalent in people over age of 35. The most common comorbid condition for people across all age groups with depression is hypertension (24%). The next most common comorbid conditions are arthritis (16%), allergies (15%) and high cholesterol (12%). Hypertension is the most common (25%) comorbid condition for people in the 35-64 age groups. [25] During the past few years, increasing attention has been paid to the prevalence and severity of major depressive episode (MDE) among children and adolescents. [26] Men recently diagnosed with depression are at double the risk of cardiovascular problems in the next five years. Comorbid conditions like depression and hypertension have high rates of morbidity and mortality. Simultaneous use of drugs to treat these conditions may cause serious drug interactions. Some antihypertensive drugs precipitate depression and some anti-depressives elevate blood pressure. How to treat these conditions in different situations needs more clinical research. [27]

COEXISTING DISEASES

An understanding of normal physiology provides the basis for elucidating the pathophysiology of disease, such as hypertension. Hypertension research has benifited enormously from physiological studies. As we enter this millennium, physiology research has yielded a rich understanding of the processes that control blood pressure and of how the dysregulation of these processes may contribute to the pathophysiology of

hypertension. To date, efforts in genetic studies of human hypertension have yielded important but limited information. [28]

The co-existing medical problems with depression are numerous. There are studies in which systolic hypertension and depression co-exist. In these patients there is higher sympathetic tone accompanied by elevated heart rates and increased levels of catecholamine. Most of the patients are evaluated and treated by primary care physician, who need to be vigilant about identifying and aggressively treating hypertension in patients who have concomitant depression. There is 156% increase in compliance with antihypertensive drug regimens in patients with high depressive scores whose family encouraged them to take their antihypertensive medication compared with depressed patients with no intervention. So there is a need to identify patients with co-existing hypertension and depression. [29] In elderly mortality related to hypertension indirectly increases with depression. [30] If depression increases, hypertension also increases making the vascular cause of death very obvious. [31] Depression is to be checked primarily when there is comorbidity like depression hypertension in a patient. [32]

Unexpected events have occurred in cardiology over the last four years. A study by the Heart and Lung Institute of the National Institute of Health in the mid 1980's showed to great surprise that class-1 antiarrhythmic drugs given to patients with ventricular arrhythmia following myocardial infarction, instead of preventing deaths actually increased the number of patients dying and since then series of studies confermed this original observation. The problem of psychiatry is that TCAs are also Class-1 antiarrythimcs. There is every reason to believe that a similar increased risk of death would exsist with the TCAs. It is therefore, important for psychiatristics to understand the cause and the magnitude of this excess in deaths. Evidance to date suggest that all Class-1 compounds, inspite being powerful antiarrythmics under usual physiological conditions, become proarrhythmic under anoxic conditions. Such conditions would exist in ischeamic heart disease during angina and particularly myocardial infarction. [33]

Various disease states are associated with altered pharmacokinetics of antidepressants. Hepatic cirrhosis causes considerable portocaval shunting; leading to increased drug concentrations, thus lowering of the usual dose of TCAs are recommended for patients with significant hepatic dysfunction, [34] chronic renal failure has little or no effect on disposition of parent compounds and demethylated metabolites. Conjugated and un-conjugated hydroxyl metabolites, however, can be markedly increased in patients with impaired renal function. [35]

CLINICALLY RELIVENT DRUG-DRUG ITERACTION

Drug-drug interactions (DDIs) are the subset of the internal environment in which the presence of second drug alters the response of first drug. DDIs can be classified as either pharmacodynamic or pharmacokinetic. Pharmacodynamic DDI is where the independent effects of the two drugs produce a change in the nature, magnitude or duration of the effect expected from either drug alone. Pharmacokinetic DDI is where one drug alters PK of a coprescribed drug (i.e, its absorption, distribution, metabolism or elimination). In a pharmacokinetic DDI one drug may be conceptualised as a victim (i.e, the effected drug) and the other as a perpetrator (i.e, the causative agent). [36]

There were 904 eligible interactions, involving 9509 patients, for a total of 598 interactions. Of these, 439 (73%) demonstrated an interaction, 148 (25%) had no effect, and 11 (2%) had conflicting evidence. For 510 interactions (85%), the quality of evidence was poor. It was fair for 67 (11%) interactions and good for 10 (2%) interactions. There were no interactions with excellent quality of evidence. There were 145 (24%) interactions of major clinical significance. These were predominantly hypertensive emergencies and serotonin syndrome. Most interacting drugs had central nervous system (CNS) activity. As expected, monoamine oxidase inhibitors (MAOIs) appear to be the most problematic family in terms of potential for serious drug interactions [37]

From public health perspective the clinical relevance of DDIs has gained increasing attention as a specific risk issue over the last 15 years initially as a result of the problisms encountered with terfinadine (seldane) which eventually lead to its removal from the market in the US and most other countries around the word. To be at potential

risk of DDI, a person must be taking more than one drug. This is common in US and the rest of developed world. To illustrate this point a "2004 US Public Health Survay" found that 44% of all Americans 18 years of age or older took one or more prescription drug in the last one week, 17% took three or more, 7% took five or more and these numbers are approximately 2 to 3 times higher for Americans 65 years of age or oldr. Based on a recent survey, antidepressant use predicts more multiple medication use than dose age in Veterans Administration (VA) Health Care System. [38] In populations of 1000 or more, 62 and 96% of the VA outpatients under 60 or older, were on unique drug combinations. Admittedly, the VA patient population may be more complicated in terms of both psychiartric and medical comorbidity than many other clinical populations. Surveys show that mosty clinical populations contain a sizable percentage that is at risk for DDI. For example, 30 to 35% of patients in primary care and private out patient psychiatric clinics are taking three or more drugs in addition to their antidepressants. [39] In summary, the sizable percentage of the US population at risk for a DDI is increased if the patient is on an antidepressant. Most of the drugs are given to change the biology of the patient. The studies carried out in VA out patients found that 83 to 96% of those on antidepressants are biologically unique based on just the specific combination of medications that they are receiving. [40] Much research has been carried out into potentially hazardous interactions with psychotropic drugs yet there is much that remains unknown. The evidence for some potential interaction is based on animal experiments, isolated case reports in which there are doubt about the cause and effect relationships or small-scale volunteer studies that may not reflect the action or an interaction between drugs in patients. It is the pharmacological and host factors that determine whether or not an individual will have a particular interaction. [41] There are many drug interactions with antihypertensive agents and some of these are highly significant. Patients with hypertension frequently take multiple medications and may be at increased risk for drug interactions. Nearly every elderly patient with multiple medical problems will have the potential for one drug interaction in their regimen. These drug interactions can lead to morbidity or even mortality if appropriate steps are not taken to minimize this risk. Drug interactions may occur due to pharmacokinetic (i.e. absorption, distribution, metabolism, elmination) or pharmacodynamic interactions. Physicians and pharmacists must remain vigilant in monitoring of potential drug interactions and make appropriate dosage adjustments. [42] Multiple medication use is a common phenomenon especially in patients with co-morbid conditions and those treated with psychiatric drugs such as anti-depressants. Combination treatment may result in potentially harmful drug-drug Interaction (DDIs). Result of DDIs range from nuisance side effects to serious adverse consequences. DDIs may also result in improved efficacy. Pharmacokinetic DDIs occur when a second drug alters the absorption, distribution, metabolism, or clearance of the first drug. The risk of harmful DDIs can be reduced by recognising variables that effect dose, concentration, effect relationships. [43]

BIOLOGICAL VARIANCE

To optimize drug therapy and reduce adverse events, it is critical that the information on how various intrinsic factors (age, gender, race, genetics and others) and extrinsic factors (concomitant medication and others) [(44)] may affect drug treatment, be available for healthcare providers and patients. There are four major sources of biological variance among Patients i.e genetic, age-associated changes in physiology, changes brought about by what the patient consumes and thus modify his internal environment. Genetics is the triat phenomenon where as the other three are the state phenomena. [45] Changes in pharmacokinetic parameters reflect systemic exposure such as area under the plasma concentration-time curve (AUC) or maximum plasma concentration, as a result of various extrinsic and intrinsic factors. The clinical significance of altered systemic exposure resulting from these factors, including genetics depends on the concentration-response relationship for both efficacy and toxicity. [46] Long term administration of amitriptyline as compared to single dose administration showed bias towards a higher mean apprant oral clearance in normal subjects, than that calculated in depressed patients. Broad individual variation in elimination rate of amitryptiline has been confermed but could not be

attributed to the clinical characteristics of the subjects. [47]

There is an increased inter-individual variability in PK/PD of drugs as people get older. There is reduction in renal and hepatic clearance and increase of volume of distribution of lipid soluble drugs. [48] As a consequence of age related changes in body composition, polar drugs, mainly water soluble, tend to have smaller volume of distribution resulting in higher serum levels. [49] Pharmacokinetics studies on the effect of aging on drug absorption have provided conflicting results. While some studies have shown reduction [50] others show increase. [51] Reduction in first-pass metabolism is due to reduction in liver mass and blood flow [52]. As a result bioavailability of drugs can significantly increase. [53] On the other hand first-pass activation might be slowed or reduced [54] for drugs that need to be activated in the liver. The total number of receptors seems to be maintained but the post receptor events are changed because of alterations of the intracellular environment. Reduced β – adrenoceptor function [55] is observed with advancing age.

PERSONALIZED MEDICINE

Personalized therapeutics has been a challenge in today's clinical psychiatry. Drug responses are complex under the control of multiple genes, environmental factors, and drug-drug and drug-food interactions. An individual's response to a drug depends on a complex interplay between environmental and genetic factors, alone or in combination. Classical family studies provide some information. [56] Twin studies have shown that drug metabolism is highly heritable with genetic factors accounting most of the variation in metabolic rates for many drugs. [57]

Antipyrine is metabolized by CYPs and the t½ between the monozygotic (identical) twin pairs in comparison to the dizygotic (fraternal) twin pairs, is having greater concordance. Comparisons of intra-pair *vs* inter-pair variability suggests that approximately 75% to 85% of the variability in pharmacokinetic half lives for drugs that are eliminated by metabolism is heritable. Heritability can be checked by inter- and intra-subjects and can be used in drug disposition in unrelated individuals. [58] Pharmacogenetic studies of drug metabolism to a broader context discuss the genetic control at multiple levels of the pharmacokinetic and pharmacodynamic pharmacologic cascade, from drug absorption and transport to drug-receptor interface and beyond. SNPs are valuable biomarkers to elucidate the genetic basis of common complex diseases and pharmacologic traits. Drug metabolism is one of the pivotal factors, which contribute to variability in pharmacokinetics. [59] A recent analysis of over 300 drugs from diverse therapeutic classes such as psychotropic analgesics and anti-infective agents found that 56% of them primarily depend on CYPs for their metabolic clearance. Among CYPs, the largest contributions are made by CYP3A4 (50%), CYP2D6 (20%), CYP2C9 (15%) and CYP2C19 (15%). [60] DNA sequence variation (polymorphism) in genes for drug metabolizing enzymes, drug receptors, drug transporters and molecules involved in signal transduction pathways may have major effect on the efficacy or toxicity of a drug. [61] High variability in the metoprolol area under the plasma concentration-time curve was associated with CYP2D6 genotypes but there was no association between CYP2D6 genotype and drug association adverse effects or antihypertensive response rate/blood pressure changes. [62, 63] Unlike traditional TDM, pharmtheracogenetic drug monitoring (PDM) – TDM based on patients pharmacogenetic information-enables clinicians to optimize dosage regimens in a noninvasive manner before drug administration. In these aspects, PDM would be complementary to the current TDM. [64]

THERAPEUTIC DRUG MONITORING

Current approaches to therapeutic drug monitoring (TDM) do not fully address pharmacodynamic variability's in patient's response to drug therapy. [65] The rational for TDM is based on putative plasma concentration-clinical effectiveness relationship that was observed for some drugs and on the observation that pharmacokinetic factors may be, in part, responsible for non response of many patients and for the occurance of adverse effects at usual doses. Measurement of pharmacokinetic alterations, either as a result of pharmacogenetic or pathophysiological reasons, is important aspect of therapeutic stratigy. The change may influence the fate of the drug and thereby the aim of the treatment. Therapeutic grug monitoring and

recommendations by the laboratory are subservient to the fact that the phycian possesses adequate information of patient's clinical situation. Preliminary evidane shows that individual patients may have their own optimal plasma drug concentration rangespossibily because because of clinical or biologic particularities [66].

Amitryptyline, a tertiaryamine Tricyclic antidepressant, is structurally related to both the skeletal relaxant cyclobanzapine and thioxanthene antipsychotica such as thiothixene. It is extreme sedating and thus improvement of sleep paterns can be the first benefit of treatment. Amitrypyiline exhibits strong anticholonergic activity, cardiovascular effects including orthosatic hypotension, change in heart rethym and conduction and lowring of seizure threshold. As with other antidepressants, several weeks of the therapy may be required in order to release the full clinical benefit of amitriptyline. Although not a labelled indication, amitriptyline is widely used in the management of chronic non-malignant pain i.e. post-herputic neuralgia, fibromyalgia. [67] TCAs toxicity, in contrast to the other major classes of antidepressant drugs, is the ability to stabilize electrically excitable membranes through the inhibition of sodium conductance (i.e, blockade of sodium fast channel).This action is responsible for their cardiotoxicity and lethality in over dosage [68]. The most characteristics and seizure sequel of this mechanism of action involves slowing of cardiac conduction, manifested as prolongation of the QT interval, intraventricular conduction defects, and AV block leading to malignant block. [69] Cardiac Arrhythmia Supression Trial (CAST), which demonstrated an increased mortality in patients treated with antiarrhythmic drugs.In this long term follow up study, patients with cardiac arrhythmias and those suffering an acute myocardial infarction were more likely to have fatal outcome if they were being treated with an antiarrhythmic drug of the type 1A class, [70, 71]

POPULATION PHARMACOKINETICS

Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population, receiving clinically relevant doses of a drug of interest. [72] Generally population analysis is far more complex than single subject approaches. The *PK* parameters depend on demographic physiological covariates such as renal insufficiency, diabetes, age, sex and weight and this finally affects the dose. There are various factors like variation in response, protein binding and P-glycoprotein that modify the *PK/PD* of a drug [73, 74].

Certain patient demographical, pathophysiological and therapeutical features, such as body weight, excretory and metabolic functions and the presence of other therapies can regularly alter dose-concentration relationships. For example, steady state concentrations of drugs eliminated mostly by the kidney are usually greater in patients suffering from renal failure than they are in patients with normal renal function, who receive the same drug dosage. Population pharmacokinetics seeks to identify the measurable pathophysiological factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shift in the therapeutic index, dosage can be appropriately modified. In contrast to traditional pharmacokinetic evaluation, the population PK approach encompasses the collection of relevant PK information in patients who are representative of the target population to be treated with the drug. [75]

Population study samples are representative than the individual, as a unit of analysis for the estimation of the distribution of parameters and their relationship with co-variates within the population. The approach uses individual PK data of the observational (experimental) type, which may be sparse, unbalanced and fragmentary, in addition to or instead of, conventional PK data from traditional PK studies characterized by rigid and extensive sampling design (dense data situation). Analysis according to the non-linear mixed-effects model [76] provides estimates of population characteristics that define the population distribution of the PK and or PD parameter. [77] Population PK findings can be useful in the drug development process and should be considered where appropriate. In drug development, population PK helps to increase understanding of the quantitative relationship among drug input patterns, patient characteristics and drug disposition [77]. This approach is useful when one has to identify factors that affect drug behaviour. It

can also explain variability in a target population. The population PK approach can be used to estimate population parameters in phase 1 and phase 2b of clinical drug development where information is gathered on how the drug will be used in subsequent stages of drug development. [77]

ANALYSIS MODELS

PK/PD models are numerous but their basic mechanism is to relate the ADME to the pharmacological action of the drug so it relates the drug levels with the dynamic response. Overall the models are easy to assemble but are useful and relevant. Physiological based pharmacokinetic (PBPK) model is the simplest model that relates organ or tissues structures to the physiology of the organ or tissue. Each organ or tissue of discrete volume is perfused by blood, a homogeneous medium that is connected to the central volume by flow. Venous equilibration is assumed, as venous drug concentration to be in equilibrium with that in the organs [78] since the organ-tissues are interconnected by the circulation [79]. Several important variables, including blood flow, plasma and red blood cell binding and transporter and enzyme activities have been identified as the determinant of organ clearance. Simple PBPK models have been applied to describe data from the liver, kidney, intestine and whole body. [80] Circulatory models were introduced into pharmacokinetics more than 25 years ago but less than 1% of the models analyze clinical pharmacokinetic data that obey circulatory structure. Decisive question is not the truth of the model but their adequacy for solving a certain task, or according to an often-quoted statement by George Box: “all models are wrong but some are useful.” A drawback of conventional models is that these compartments lack physiologic reality. A condition that limits the complexity of models of solute distribution in the body is that they must be theoretically and practically identifiable, while remaining consistent with known physiology. An implicit assumption in the use of the term “circulatory” pharmacokinetic model is that the parameters can be estimated on the basis of plasma concentration-time data, and are readily applicable to clinical data. The so called Physiologically Based Pharmacokineric “PBPK” Model is too complex for identification on the basis of plasma concentration-time data alone. [81] Circulatory models are applied to those drugs which are fast acting to evaluate distribution kinetics. This is used in knowing the onset and offset of action. Modelling of drug distribution kinetics within first 2 minutes (front end kinetics) determines the induction dose of intravenous anaesthetics. [82] A re-circulatory model with a chain of compartmental sub-system that adequately characterizes pulmonary first-pass distribution and intravascular mixing has been applied to analyze the kinetics of insulin, antipyrine, lidocaine, and thiopental. [83]

A *PK*/*PD* analysis of rocuronium [84] showed that circulatory models accounted for the effect of cardiac output and allowed an improved estimation of pharmacodynamic parameters. Such model can be applied to propofol and fentanyl. [85] Circulatory models can tell about difference of plasma concentration within vascular space. Portal and systemic blood samples were simultaneously taken to evaluate the intestinal absorption [86] and characterise role of the liver. The transient concentration difference between arterial and peripheral venous blood concentration on the other hand, have to be taken into account in *PK*/*PD* modelling. One of the most important out comes in pharmacokinetic modelling is thw ability to predict grug levels and/or dynamic behaviours of drug entities in the body. Another is the deduction of mechanistic insight in to what events have happned. Some times the question is not how realistic the models are but what is their consistency and adequacy in making predictions. Most models are over simplifications of the reality. It is vertainty the hopes of pharmacokinetists that the models are easy to assemble, useful and relevant. [87]

There is the departure from the compartmental modelling to physiological modelling in order to confer more significance to the anatomy, flow and discrete eliminatory and/or distributional organs in the body. [88]

SUMMARY

Valuable and reliable information may be extracted from TDM collected samples. The TDM databases are valuable tools for collecting new PK-data from large scale heterogeneous clinical populations after the introduction of a drug into the

market. Thus the development of a drug should be seen as a continuous process. The data collected by the TDM service may improve refrence data for the evaluation of therapeutic response as well as toxicological information concerning in psychoactive drugs [89].

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