CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Pharmacology is the science of drugs. It contributes to the development of drugs, the understanding of their mechanisms of action and the description of their conditions of use. It also deals with the assessment of their efficiency (through clinical trials) and their safety (through pharmacovigilance). Administration, legislation and complex control systems characterize this field which is at the crossroads between research and development (in the Pharmaceutical industry) and so-called basic research.

Pharmacology is an indispensable prerequisite for the learning of therapeutics and continuous flexibility is needed to move from collective data (pharmacology of populations, clinical pharmacology) to the individual conduct required in a precise case. It is also necessary during the pharmacokinetic monitoring of a specific case. The application of pharmacoepidemiology data to an individual patient is linked to the interpretation of statistical data.

Because Pharmacology is continuously evolving, it is an excellent training ground for research, especially in the clinical fields. It concerns all practitioners of medicine, whatever their field may be. Moreover, it calls for the use of techniques from many other specialities, such as biochemistry, epidemiology, statistics and others.

Pharmacology possesses its own vocabulary, institutions, laws and regulations, not to mention the basic rules regarding drug usage and the prescription of medicines, which must first be learnt. A good knowledge of the placebo and nocebo effects is necessary before continuing the study of active molecules. Some general remarks (which will have to be read again during the study of drugs in specialized medical fields) will describe the official methods required to define the pharmacokinetic profile of products, to carry out (or to participate in) clinical trials and to analyse the results of pharmacovigilance and pharmacoepidemiology (meta-analyses). These points are relevant from the beginning of clinical training at the hospital and also afterwards in medical practice. They can be summarised in the following equation:

Pharmacology = a guide for therapeutics = a method to optimise therapeutics.

Pharmacology is a fabulous tool for research, since drugs are, thanks to their specific mechanisms of action, real probes which can help decipher the innermost mechanisms of
physiology. This is perfectly illustrated by neuropsychopharmacology, which is the basis of understanding behaviour and, why not, even ideas! At a fundamental level, it also helps to create models.

Pharmacology has good prospects, since drugs of the future will be the result of biotechnology (gene therapy) or the final result of improvements in galenics. Pharmacology does have a cost, but if well controlled it may contribute to savings in Public Health (pharmacoeconomics). It is also a source of bioethics, as well as making us question the new technologies available for the broadcasting and dissemination of new information. Finally, Pharmacology contributes to the evidence-based approach to medicine.

1.2 PHARMACOKINETIC/PHARMACODYNAMIC MODELING CONCEPT

Pharmacokinetics involves the kinetics of drug absorption, distribution, metabolism and excretion, or in other words, it is defined as the use of mathematical models to quantitate the time course of drug absorption and disposition in man and animals (Riviere, 1999). Pharmacodynamics has been defined as the study of the biologic effects resulting from the interaction between drugs and biologic systems (Holford and Sheiner, 1981). Modeling “provides a systematic way of organizing data and observations of a system at cell, tissue, organ, or whole animal (human) levels” and “affords the opportunity to better understand and predict physiological phenomena” (Epstein, 1994). Pharmacokinetic/pharmacodynamic modeling has been used as a tool to understand the impact of dose or drug concentration on pharmacological response.

Assuming a compartmental structure, pharmacokinetic models can be written in form of sums of exponentials, or differential equations based on mass-balance, or mass-action principles. For pharmacodynamics, many mathematical models have been proposed. The most widely used pharmacodynamic models are the $E_{max}$-model and the sigmoid $E_{max}$-model which are often regarded as empiric mathematical functions that describe the shape of the concentration-effect relationship for a particular drug. However, these models cannot distinguish between the occupation and the activation of a receptor by an agonist. In contrast, the operation model proposed by Black & Leff (1983) can relate receptor occupancy and pharmacologic effect using two successive saturable hyperbolic
functions. The first is the binding of the agonist to the receptor, and the second is the stimulus-response relationship between the agonist-receptor complex ([AR]) and the pharmacological effect (Kenakin, 1993). The PK/PD modeling is a mathematical approach that correlates the mass transfer embedded in pharmacokinetic model to drug effect (Riviere, 1999). The drug effect cannot be directly correlated to the drug concentration in a pharmacokinetic compartment, since due to an equilibrium delay with the site of drug action (Sheiner et al., 1979) or post receptor transduction system (Mager and Jusko, 2001), it becomes necessary to identify a biophase as an effect compartment so that concentration-time profile in biophase can be correlated to drug effect.

Model parameters estimated are normally built using experimentally data that contain information on the system (systematic component) and are subject to errors. Therefore, one objective of mathematical modeling is to differentiate the systematic component in the system from the noise or random component in the system. Hence, models usually consist of a structure model that derived from systematic component plus a statistical model that describe the error component of the model (Bonate, 2006). One can choose either an empirical or mechanism-based model. The empirical model is useful when little is known about the underlying physical process, whereas the mechanism-based model is based on physical and physiological principles. Factors such as transport to tissues dependent on blood flow, kinetics of receptor binding and intracellular diffusion processes may all play a role. In order to increase knowledge in pharmacologic mechanism, researchers have established many useful mechanism-based models. For example, mechanism-based pharmacokinetic model for paclitaxel (Henningsson et al., 2001), digoxin (Baek and Weiss, 2005), idarubicin (Weiss and Kang, 2002), midazolam (Cleton et al., 2004), etc.

1.3 PHARMACODYNAMIC AND PHARMACOKINETIC PRINCIPLES OF PHARMACOLOGY AND DRUG THERAPY

Pharmacology is the study of interactions between chemicals and living tissue and provides the rational basis for therapeutics. In order to deliver the appropriate amount of drug for a reasonable length of time to achieve desired beneficial effects while
minimizing adverse effects, it is useful to consider the relationship between the drug's pharmacodynamic and pharmacokinetic properties. This research focuses on the basic principles of pharmacology whose clinical application is important in reaching a favorable risk/benefit ratio. Drugs sharing an ability to inhibit dopamine receptors in various brain regions are used to illustrate some of the principles as these drugs often cause serious neurological side effects in patients. To accomplish optimal treatment an appreciation is required of the manner in which pharmacodynamics and pharmacokinetics can be influenced by such factors as genetic makeup, age, body weight and composition, sex, environmental factors, physiological variables, and pathological factors. Understanding the manner in which changes in critical pharmacodynamic characteristics or pharmacokinetic constants result in changes in plasma levels of drugs allows practitioners to make appropriate dosage adjustment to avoid therapeutic complications.

1.4 PHARMACODYNAMIC CONSIDERATIONS

Pharmacology can be described as the study of the interaction between chemical substances and living tissue. The discipline of pharmacology is considered to be the rational basis of clinical therapeutics. The goal of therapeutics is to deliver the appropriate amount of drug for a reasonable length of time to achieve a desired beneficial effect with a minimum of adverse effects. The focus of this research will be the basic principles of pharmacology whose clinical application is important in reaching that goal as illustrated by several classes of drugs used in symptomatic treatment of psychiatric disorders. These drugs were selected for illustrative purposes because they often share a propensity to cause neurological side effects.

It is convenient in considering the pharmacology of drugs to divide the subject into pharmacodynamics and pharmacokinetics. As can be seen, pharmacodynamic processes are those that occur after the drug reaches its site of action and binds to its pharmacological receptor. The drug's pharmacokinetic characteristics that determine how rapidly a drug will appear and for how long the drug will remain at the target site of action and in the body. In actuality, once a drug is administered pharmacokinetic and pharmacodynamic mechanisms occur simultaneously. For pharmacological agents to be
effective clinically, they must be able to alter the function of a target site, cell, or organ (pharmacodynamics). At the same time, they are chemical molecules introduced into a biological system and thus have a fate or disposition (pharmacokinetics). The fundamental concepts important in understanding and employing these components of a drug's pharmacology are described below.

Pharmacodynamics consists of the drug actions, which are a sequence of steps initiated by alteration of the receptor upon drug binding followed by signal transduction steps that amplify and prolong the change in a specific biochemical or physiological system. These pharmacodynamic actions culminate in the drug's pharmacodynamic effects, which are grossly observable at an individual patient or organ level. Drug effect is often used interchangeably with drug response. Pharmacodynamics governs the concentration-effect portion of the drug and tissue interaction. It is the component that is important in the classification of a drug and the appropriateness of a drug for treatment of a particular symptom.

1.5 DRUG RECEPTORS

In most cases, in order to bring about a change in biological function, the drug molecule interacts with a specific macromolecule (receptor) that plays a regulatory role in a target tissue. Many important drug receptors are proteins that normally function as receptors for endogenous compounds, such as hormones, growth factors, and neurotransmitters. Binding of drugs to these receptors leads to propagation of a regulatory signal in the target cell. In this manner a drug is able to alter the rate at which any bodily function proceeds. The initial binding results from a structural complementarity between a receptor and the drug with an appropriate size, electrical charge, shape, and atomic composition. This 'goodness-of-fit' linking drug structure and receptor structure largely determines the affinity or binding avidity of the drug-receptor complex. Once binding has occurred, agonist drugs activate or alter the function of the receptor and other components of a signal transduction pathway, which directly or indirectly leads to the effect. Another group of useful therapeutic agents that have an affinity for receptors but, in contrast to agonists, have no ability to activate them are referred to as antagonists.
Antagonist drugs find their clinical usefulness in their ability to prevent the binding of endogenous agonists to their receptors thereby reducing their normal actions.

1.6 RELATIONSHIP BETWEEN DRUG DOSE AND CLINICAL RESPONSE

Regardless of the complexity of drug-receptor interactions at a molecular level, the relationship between the dose administered and the response elicited can be described relatively simply. There are 2 types of dose-response relationships commonly encountered. Graded dose-response curves describe the relationship that is observed in individual patients or single test subjects (an animal, an organ, a cell) as increasing doses or concentrations of drug are administered. In contrast, quantal dose-response curves analyze the effect of administering increasing doses to populations of test subjects.

1.7 ABSORPTION

The rate and extent of absorption of drug following different routes of administration can be quite variable. Often these differences are exploited for therapeutic advantage since they influence the duration and intensity of drug action. Absorption following oral administration can be quite erratic, incomplete, and differ from individual to individual. In such situations, patient-to-patient differences in side effects may be exaggerated. For example, even though antipsychotic agents are highly lipophilic, they can have unpredictable patterns of absorption that may contribute to interpatient variability in the occurrence of neurological side effects. However, its convenience and economic advantages coupled with the potential for design of specialized drug delivery systems like enteric-coated or timed-release medications makes it the most common method of drug administration. Drugs may be administered sublingually where they pass through the oral mucosa into the venous drainage from the mouth and into the vena cava and are therefore protected from rapid inactivation by liver enzymes. Drugs are often given by parenteral injection such as intravenous, subcutaneous or intramuscular. Absorption of drug from the latter two sites occurs by simple passive diffusion along its concentration gradient. The rate is limited by the area of the absorbing capillaries and by the solubility of the drug in the interstitial fluid. Intravenous administration circumvents absorption, since the drug is introduced directly into the blood. This route not only provides the desired
concentration of drug in the blood immediately and very accurately but also allows titration of the dosage. The drug absorption from each potential route of administration has its own characteristic pattern, special utility, as well as, limitations and precautions.

1.8 DISTRIBUTION

After absorption, the drug may be distributed into interstitial and cellular fluids. The pattern of drug distribution is a consequence of certain physiological factors and physicochemical properties of the drug. If the drug is given intravenously, an initial phase of distribution may be seen that reflects regional differences in rate of blood flow. Heart, liver, kidney, and other highly perfused organs may receive most of the drug shortly after administration. The delivery of drug to other more slowly perfused tissues, such as muscle, skin, or fat may take from 30 minutes to many hours to reach equilibration with the bloodstream. Antipsychotic drugs tend to be highly lipophilic since their access to receptor sites requires they pass the blood-brain barrier and they also enter the fetal circulation and breast milk. Once equilibration has been achieved, the drug occupies a space equivalent to different physical compartments of the body. In addition, drug molecules may be bound to cellular proteins or dissolved in fat or sequestered by cell surfaces or bone. These compartments represent the potential volumes in which the drug may occupy. If the total amount of drug present in the body is divided by the measured plasma concentration of drug the apparent volume of distribution is obtained. It is this volume that is used in pharmacokinetic calculations of dosage regimens, loading doses and the setting of steady state blood levels that lie within the therapeutic window.

1.9 RATIONAL DOSING AND THE TIME COURSE OF DRUG ACTION

In setting dosage regimens, it is assumed that there is an appropriate target concentration at the drug's site of action that will produce the desired therapeutic effect. Furthermore this target concentration is controlled by the concentration of drug in the bloodstream, which is determined by the drug's pharmacokinetic parameters (half-life, apparent volume of distribution, and clearance). Clearance is the volume of plasma that has been cleared of drug by all the routes of elimination. It is usually expressed as ml/min. For example, propranolol is cleared at the rate of 840 ml/min almost entirely by the liver.
This means that the liver is removing all the propranolol from 840 ml of plasma every
minute. Clearance can be calculated by dividing the rate of a drug's elimination by its
concentration in plasma.

Clearance is often the pharmacokinetic parameter affected by changes in disease states,
enzyme induction, altered glomerular filtration, or the aging process, which result in
altered responses in individual patients. In addition, since a certain volume of plasma is
being cleared of drug per minute, drug must be administered again at a dose and time
calculated to replace the amount of drug that has been cleared. This is done with the
intent of maintaining a steady state concentration of drug in plasma within the therapeutic
range.

Whenever first order kinetic drugs are given in multiple fixed doses or by intravenous
infusion, the drug will accumulate in plasma until a steady state is reached. At this time,
the rate of drug administration will be equal to the rate of drug elimination. In most
clinical situations, drug administration aims to maintain a steady state level of drug in the
plasma that will achieve the appropriate target site concentration. The time course of drug
accumulation and elimination for a drug given by intravenous infusion. The time course
of accumulation for a drug given at fixed doses and fixed time intervals. In both
situations, it can be seen that the concentration of drug in plasma increases until a steady
state is reached. The clinical objective is to employ a suitable dose and dosage interval to
insure that the eventual steady state achieved is within the therapeutic range.

For drugs administered by intravenous infusion, the relationship between drug infusion
rate and steady state plasma level is predicted from the following equation.

\[ \text{Css} = \frac{\text{infusion rate}}{\text{ke} \times \text{Vd}} \]

Where \( \text{Css} \) is the plasma concentration at steady state, \( \text{ke} \) is the first order rate constant
for elimination (0.693/half-life) and \( \text{Vd} \) is the drug's apparent volume of distribution.

For drugs administered orally at a fixed dose and dosage interval, the relationship
between steady state and dosage rate is given by the following equation.
\[ \text{Css} = D \times F_{\text{ke}} \times V_d \times T \]

Where \( D \) is the single unit dose, \( F \) is the bioavailability, and \( T \) is the dosage interval.

As mentioned above, common side effects of antipsychotic treatment are a variety of neurological syndromes. Since symptoms such as akathisia are difficult to treat they may significantly interfere with the acceptance of neuroleptic treatment. From inspection of the steady state equations above, it can be seen changing the dose and/or the dosage interval will decrease (or increase) the blood level of a drug. This often represents a rational approach to manage the extrapyramidal symptoms. Following initiation of therapy and suppression of psychotic symptoms attempts to lower blood levels to a level that maintains relief of symptoms while decreasing the severity of neurological side effects may be appropriate.

Following drug administration it is important to know the length of time needed for a drug to accumulate to its eventual steady state. The general rule is that it takes 4 to 5 half-lives following the initiation of drug therapy to reach a steady state concentration of drug in plasma. A drug with a half-life of 5 hours will reach its steady state (>90%) in about 20 to 25 hours and a drug with a half-life of 10 hours will reach its steady state in about 40 to 50 hours. The inevitable time required for a drug to accumulate to steady state can be circumvented by giving a loading dose and then switching to a maintenance dose. It is similarly true that once drug administration is stopped it requires about 4 to 5 half-lives to eliminate a drug, so that a drug with a 5-hour half-life will be eliminated in about 20 to 25 hours while one with a 10-hour half-life will require 40 to 50 hours.

**1.10 CLINICAL RELEVANCE OF BASIC PRINCIPLES**

Practitioners have recognized for a long time that individual patients show a wide variability in response to identical drug treatment protocols. The progress made in understanding the sources of this variability has encouraged individualization of drug therapy. To accomplish optimal treatment an appreciation is required of the manner in which pharmacodynamics and pharmacokinetics can be influenced by such factors as
genetic makeup, age, body weight and composition, sex, environmental factors, physiological variables, and pathological factors.

In considering the variable of age, it has long been assumed that elderly patients are more sensitive to a variety of drugs due to changes in the pharmacodynamics of the drug-receptor interaction. Clinical studies suggest that elderly patients are more sensitive to certain sedative-hypnotics and analgesics. For example, elderly patients who were given diazepam for a surgical procedure required lower doses than younger patients to reach the same level of sedation. There are numerous sites of pharmacodynamic action that may alter drug response with aging, including a change in the number of receptors, a change in the affinity of the drug for the receptor, or a change in the responsiveness of signal transduction pathways. Monitoring sensitivity to [beta]-adrenergic agonists using the production of cyclic 3',5' adenosine monophosphate by lymphocytes as an indicator of responsiveness to isoproterenol demonstrated a decrease in adenylate cyclase in subjects of ages 67 to 90 as compared with those of 18 to 27 years. Other studies also have found a decrease in the responsiveness of [beta] receptors in the elderly even in the absence of any decline in receptor numbers.

It is now recognized that most of the differences in sensitivity to drugs in the elderly result from changes in pharmacokinetics. There are many changes associated with aging that could potentially influence drug disposition. Since most drugs are taken orally, documented age-related increases in gastric pH, decreases in gastric emptying, decreases in absorptive surfaces, and lowering of intestinal motility could alter drug absorption. Following absorption, the distribution of the drug may be different in older patients since they have less lean body mass, decreased total body water, and increased body fat. Thus, the volumes of distribution of water-soluble medications and fat-soluble medications are decreased and increased, respectively. These changes will be reflected in alterations in blood levels of the drugs and changes in the drugs half-life. For example, the fetus, the infant, and the elderly have a diminished capacity to biotransform and eliminate antipsychotic agents. This decreased capacity results in a lowering of the rate constants used in establishing maintenance doses and a subsequent increase in blood levels. The higher blood levels can increase the incidence and severity of neurological motor
symptoms. In addition, the dose calculations include a term for the volume of distribution whose value is most often determined in young healthy adults but can be adjusted to be age-specific for dosage regimen calculations.

The equations used for dose and dose interval determinations always include a term for the rate of elimination. However, in elderly patients the 2 main routes of drug elimination are often slowed. Biotransformation in the liver depends upon hepatic blood flow and the activity of the liver enzymes responsible for the biotransformation of the drug. Age-related declines in both liver mass and hepatic blood flow may lead to altered drug disposition. These changes result in a decrease in the clearance of the drug and a prolongation of its half-life. From inspection of the dose calculation equations, it is clear that if the dose is not changed the result of these alterations in biotransformation will be an elevation in the steady state concentration of the drug in plasma and a corresponding increase in pharmacological effect. Decreases in biotransformation can lead to a marked increase in the half-life of certain compounds. Ordinarily, diazepam is converted to desmethyldiazepam an active metabolite that accumulates when its biotransformation is decreased. Due to its long half-life, it can take weeks to reach its eventual steady state in plasma and may lead to a continuing increase in sedation in the elderly patient over time.

Excretion of drugs by the kidney provides the eventual pathway for the elimination of most therapeutic agents. The age-related changes that potentially affect this function include decreased renal blood flow, decreased glomerular filtration rate, and decreased renal tubular secretion. These changes will decrease the clearance of a drug and, if the dose is not adjusted, lead to an increase in the plasma drug concentration. These effects are particularly important for drugs with narrow therapeutic indices whose elimination is primarily renal. Certain drugs, eg, aminoglycoside antibiotics, are not only eliminated solely by renal elimination but are themselves nephrotoxic. Dosage adjustment based on the state of renal function is mandatory when prescribing such drugs to the elderly. The decreased renal function results in alterations in the pharmacokinetic parameters that are used in dosage calculations. Understanding the manner in which changes in critical pharmacokinetic constants result in changes in plasma levels of drugs allows practitioners to make appropriate dosage adjustment to avoid therapeutic complications.
AREAS CONSIDER FOR PRESENT RESEARCH

Mathematical Models apply in Clinical Trails, Bioavailability and Bioequivalence, Cancer incidence and survival analysis. Live example is given in Chapter 4 for BA/BE study.

1.11 ORGANIZATION OF THE THESIS

The first chapter contains the introduction, pharmacokinetic/pharmacodynamic modeling concept, pharmacodynamic and pharmacokinetic principles of pharmacology and drug therapy, pharmacodynamic considerations, drug receptors. Relationship between drug dose and clinical response, Rational dosing and the time course of drug action and clinical relevance of basic principles.

The second chapter is devoted on Demographic details of India like Population characteristics, Population growth birth and death rates, Age distribution, Life expectancy at birth and urban rural distribution, cause of death, measures of disease occurrences, Trends in Incidence, Clinical medicine also described trends of cancer incidence. Cancer mortality and projection of increased in cancer incidence.

The third chapter describes Mathematical modeling for Pharmacology like Epidemiological, Toxicological, Armitage-Doll multistage Model, Pharmacokinetic Modeling.

The fourth chapter contains basic considerations of Pharmacokinetics and also covers various Models like Zero order Kinetics, First-Order Kinetics, Mixed-Order Kinetics, compartment Models, Noncompartmental Models and Physiologic Models. In this chapter we have also try to focus of Bioequivalence of two oral formulations of Felodipine Tablets in healthy male volunteers.

The fifth chapter shows the interdisciplinary relationship with emerging Compartment Modeling in Pharmacology like One –Compartment Open Model, Two -Compartment Open Model in Intravenous bolus administration and Extravascular administration.
The **sixth chapter** is based on survival analysis techniques for Pharmacology like Estimates of the Variance of the Kaplan-Meir Estimator, Hypothesis test and confidence interval based on asymptotic normality, Parametric and nonparametric methods, some problems with the Kaplan-Meir Estimator, Startified analyses and planning a study to control standard error.

The **seventh chapter** deals with Statistical techniques for Clinical Trials to determine sample size and sensitivity of index, Trial design considerations, The selection of dose, the technique to avoid biasness, Interim analysis, Analysis of BA/BE study and Analysis of Clinical Trial study.

The **eighth chapter** caters to Various General Linear model like Maximum Likelihood Estimators using Log-Linear Models, General Linear mixed Models also shows practical applications of regression models, link function and variance structure.

The **last and final chapter** is conclusion of these entire studies. It covers major findings, valuable suggestions, areas for future enhancement and scope in the areas of research.