Report on
All India Council for Technical Education (AICTE), New Delhi, Sponsored
Quality Improvement Program (QIP)
Short Term Course on
Bio Pharmaceutical Approach Based Drug Delivery Systems and Regulatory Challenges
&
Applications of Pharmacokinetics in Clinical Practice
(15th – 27th September 2014)

Program Organized
by
Dept. of Pharmaceutics
JSS College of Pharmacy
Udhagamandalam-643001. The Nilgiris.

Report by:
Dr. K. Gowthamarajan,
Professor and Head, Dept. of Pharmaceutics

Submitted to
JSS University, Mysore

Report on
All India Council for Technical Education (AICTE), New Delhi, Sponsored
Quality Improvement Program (QIP)
Short Term Course on
Bio Pharmaceutical Approach Based Drug Delivery Systems and Regulatory Challenges

Report submitted by: **Date:**

Dr. K. Gowthamarajan
Professor & Head / QIP Program Coordinator
Dept. of Pharmaceutics

15 – 20th September 2014

15.09.2014 (Day I - Monday)

A week long All India Council for Technical Education (AICTE), New Delhi sponsored Quality Improvement Program (QIP), Short Term Course on Bio Pharmaceutical Approach Based Drug Delivery Systems and Regulatory Challenges and Applications of Pharmacokinetics in Clinical Practice was organized by Dept. of Pharmaceutics from15th to 21th September 2014.
Dr K. Gowthamarajan, Professor & Head, QIP – Program Coordinator welcomed the participants of the QIP and introduced the program to the participants. Further, he also introduced the team members of the QIP program and topics to be covered during the program.

Session – 01:

Topic: Lipid based drug delivery systems (LBDDS)

Presenter: Mr. R. Suresh Kumar, Asst. Professor, Dept. of Pharmaceutics

About 40% new molecular entities (NMEs) display low solubility leading to poor bioavailability, high intra subject/inter subject variability and lack of dose proportionality. Therefore, producing suitable formulations is very important to improve the solubility and bioavailability. Solid ispersions, Micronisation, Salt formation etc.In recent years, much attention has focused on lipid based formulations. The most popular approach is the incorporation of the active Lipophilic component into inert lipid vehicles such as oils, surfactant dispersions, nanoemulsions etc. Self nanoemulsifying drug delivery systems (SNEDDS) are simple to prepare and evaluate. Moreover This system does not change the characteristics of drug instead utilizes the same lipophilic character for solubilisation.

Session – 02:

Topic: Phytosomes – A novel approach for delivery of phyto constituents

Presenter: Dr. D. Nagasamy Venkatesh, Asst. Professor, Dept. of Pharmaceutics

Medicinal plants have been known for many decades and highly recognized as rich source of therapeutic agents, health promoting benefits of numerous botanical properties for the prevention and treatment of diseases and ailments. Over the past century, chemical and pharmacological sciences established the composition, biological activities and health giving benefits of numerous plant extracts. Recently, greater focus has been devoted in developing a drug delivery system for herbal medicines by a scientific approach. It is a novel emerging technique applied to phytoconstituents for the enhancement of bioavailability for medicinal applications. The term "Phyto" means plant, while "somes" means cell-like. This is technique was developed by Indena spa, Italy. They identified that the incorporating phospholipids into the standardized extracts so vastly improves absorption and utilization of phytoconstituents. Phytosome acts itself like a small cell and protects the valuable components of the herbal extracts being protected from destruction by the digestive secretion and gut bacteria. Water-soluble phytoconstituents can be converted into lipid a compatible molecular complex that facilitates herbal extract to pass through effectively lipid rich biomolecules. Over the past century; phytochemical and phyto-pharmacological sciences established the compositions, biological activities and health promoting benefits of numerous botanical products. Many of the biologically active constituents of plants are polar or water soluble molecules. However, this water soluble constituents (flavonoids, tannins, glycosidic glycones), are poorly absorbed due to their poor lipid solubility, large molecular weight causes poor absorption by passive diffusion, poor lipid solubility causes rate limiting step to pass across the lipid rich biological membrane and results in poor bioavailability. Many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken oral route of administration. However, incorporating phospholipids into standardized extracts, improves their absorption and better utilization. The flavanoid and terpenoid constituents of plant extracts lend themselves quite well for the direct binding to phosphatidylcholine.

Session – 03:

Topic: Herbal Technology & Regulatory Concerns
Presenter: Dr. K. Gowthamarajan, Professor & Head Dept. of Pharmaceutics

Session – 04:
Topic: Bio-pharmaceutics approaches in drug delivery system
Presenter: Dr. K.Gowthamrajan, Professor & Head Dept. of Pharmaceutics

The case study was presented to apply the biopharmaceutical classification system to herbal medicine products with biopharmaceutics and formulation consideration for improving the dissolution and bioavailability by physical modification approach. Based on the BCS information, the selected phytoconstituents such as quercetin, curcumin and piperine except rutin were selected for further physical modification to obtain poly herbal nano preparations such as poly herbal nano crystals (NC) and poly herbal solid lipid nano particles (SLN).The results indicating that the physically modified phytoconstituents as nano crystals exhibited good dissolution profile when compared to unmodified phytoconstituents. The pharmacokinetic studies indicated that the oral bioavailability of the phytoconstituents was obviously improved after physically modified.This concept helps the formulators to know that which type of formulation strategy should be followed, more ever this BCS reduce the formulation burdens and also the dose level of the herbal drugs can also been known. Applying the principles of BCS to herbals and their constituents can help to improve the quality of herbal medicines.

Session – 05:

Topic: Herbal cosmeceuticals their formulation –regulatory Scenario

Presenter: Dr. V. Senthil, Professor

The use of cosmeceuticals has drastically risen in recent years. This significantly increases the armamentarium of the clinician in improving the treatment of skin, hair, and other conditions. They are at the juncture where wellness meets beauty and growing use by consumers is indicative of their popularity. This article focuses on skin, hair, and other cosmeceuticals and their regulatory aspects.

Today a new hot topic in the cosmetic industry is 'cosmeceuticals', which is the fastest growing segment of the natural personal care industry. Cosmeceuticals are topical cosmetic-pharmaceutical hybrids intended to enhance the beauty through ingredients that provide additional health-related function or benefit. They are applied topically as cosmetics, but contain ingredients that influence the skin's biological function. The Food, Drug, and Cosmetic Act defines cosmetics by their intended use, as 'articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance.' Among the products included in this definition are skin moisturizers, perfumes, lipsticks, fingernail polishes, eye, and facial makeup preparations, shampoos, permanent waves, hair colors, toothpastes, and deodorants, as well as any material intended for use as a component of a

cosmetic product. These cosmeceuticals, serving as a bridge between personal care products and pharmaceuticals, have been developed specifically for their medicinal and cosmetic benefits. Tracing the origin of cosmetics, the first recorded use of cosmetics is attributed to Egyptians, circa 4000 BC. The ancient Sumerians, Babylonians, and Hebrews also applied cosmetics. In other cases, such as European cosmetic known as Ceruse was used from the second century to the 19th century.

Desirable features of cosmeceutical agents are efficacy, safety, formulation stability, novelty, and patent protection, metabolism within skin and inexpensive manufacture. An attempt has been made to review the different types of cosmeceuticals and their regulatory aspects

Session – 06:

Topic: Extrusion & Spheronization

Presenter: Dr. Ganesh GNK

In present times, the pelletization technologies are giving much attention as they represent an efficient pathway for manufacture of new drug delivery system .It has good advantage over the conventional dosage form. Pelletization technique help in the formation of spherical beads or pellets having a diameter 0.5 -1.5 mm which can be eventually coated for preparation of modified release dosage form .It leads to an improvement in flow ability, appearance and mixing properties thus avoiding for generation of excessive dust and reduces segregation and remove the undesirable properties and improve the physical and chemical properties of fine powder. The pellets can be prepared different techniques such as powder layering, suspension /solution layering, extrusion and spheronization, cryopelletization, etc. Today pelletization represents an efficient pathway for novel drug delivery in the scope for different oral immediate or controlled delivery systems. Because of its simple design, high efficiency of producing spherical pellets and fast processing, pelletization has found a special position in pharmaceutical industry and especially in case of production of multi particulate oral controlled release dosage forms as compared to granulation. Pelletization technique produces more spherical pellets and offers more advantages than granulation process. In addition, hot-melt extrusion method has provided a new, wider platform to produce spherical pellets of drugs which are not stable or have compatibility problems in presence of solvents.

Session – 07:

Presenter: Dr. Jawahar. N.

Topic: Solid Lipid Nanoparticles for Brain delivery

Drug delivery to the brain is a challenge, because this tissue benefits from a very efficient protective barrier. The BBB is a major barrier to the passage of active molecules from the blood compartment to the brain due to presence of tight junctions between the brain cells. Solid Lipid nanoparticles (SLN) are novel drug delivery systems prepared to pass through such efficient barriers and target the desired site. Solid lipid nanoparticle are tiny colloidal carriers composed of biocompatible/biodegradable lipid matrix that is solid at body temperature and exhibit size range in between 100-400nm. SLN combines advantages and avoids disadvantages of other colloidal carriers like liposomes, polymeric nanoparticles and emulsions.

Among the different drugs only 5% of the drugs treat the depression, schizophrenia, and insomnia (Ghose et al.,1999) The successful incorporation of Olanzapine, a poorly soluble drug, into SLNs by an emulsification and low temperature solidification method. The preparation of solid lipid nanoparticles containing Olanzapine and its Pharmacokinetic with tissue distribution studies were carried out in rats, following i.v. administration of the OZ-Sol. Solid lipid nanoparticles prepared with different lipids and surfactants were found to be stable over period of two years. The interaction of solid lipid nanoparticles with human granulocytes has been reported that surfactant influences the velocity of phagocytosis of SLN by human granulocyt.

Session: 08
Presenter: Dr. Phani kumar: had delivered the lecture on
Topic: ANDA application process

Dr. Phani kumar had delivered the lecture on ANDA application process. An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One

way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug. The Office of Generic Drugs home page provides additional information to generic drug developers, focusing on how CDER determines the safety and bioequivalence of generic drug products prior to approval for marketing. Generic drug application reviewers focus on bioequivalence data, chemistry and microbiology data, requests for plant inspection, and drug labeling information.

Session: 09-11
Presenter: Dr. Nilani Packianathan, Dr. Sankar and Dr. R.B. Umamaheshwari

Topics: Patents Designs, Practice & procedure, PANOPIC View of IRRs and Introduction to Intellectual property rights and their economic importance – Academic & Industry perspective

The patent experts delivered the talk on patent laws and given hands on training to Indian patent filling. India is a major market with a population of 1.21 billion people (2011 census), the second most populous country in the world and is a rapidly growing economy. Starting with the Patents Act of 1970, India had opted for strong protection to its industry and particularly to its pharmaceutical industry. Consequent to India becoming signatory to TRIPS in 1998, the patent laws and rules have been amended with the latest amendments taking effect from May 5, 2006. The Annual Report of the Indian Patent Office (IPO) (June 2011) states that "the TRIPS compliant intellectual property laws in India coupled with strong enforcement mechanism and judicial system created the best investment opportunities and conducive environment for protection of IP rights in order to enable the business community to diversify their commercial activities."

The Office of the Controller General of Patents, Designs & Trade Marks (CGPDTM) is located in Mumbai. The Head Office of the Patent office is in Kolkata and its Branch offices are located in Chennai, New Delhi and Mumbai. The Patent Office receives applications at each of the four offices according to a determination of jurisdiction. For international applicants, the appropriate office is the one closest to the address for service in India, which practically goes down to the place of business of the patent agent. Electronic filing is possible with the use of a Class III digital signature through the Patent Office's Website, but requires a specific browser (Internet Explorer) with custom changes to the security settings, for the registration procedure and to set up the software

However, the electronic filing system is not yet very user-friendly and it could be challenging to complete the filing process correctly. Filing on hard copy is still the most popular way of communicating with the IPO and requires payment through demand draft or bank pay order. Acknowledgement and filing reference number are only sent by mail and may take up to a month to be mailed to the applicant. India Patent applications are automatically published after an 18-month delay from the priority date, without payment of any additional fee. However, early publication can be requested on payment of Rs.10,000 (~200 USD, Rs.2,500 or ~50 USD for individual applicants), which will result in publication of the bibliographic details and abstract of the application in the Patent Office Journal that is published weekly on every Friday on the Patent Office Website. Examination of published applications can be requested anytime after publication, but within 48 months of the earliest filing date.

Session: 12
Presenter: Dr. S.N. Raju

Topics: Industrial Career perspective
The expert from Dr Reddy's, Hyderabad deliberated the critical issues about the interview selection procedure, pre preparations and post responsibilities for successful career in reputed pharma industries.

Glimpses of some moments

Dr. K. Gowthamarajan, Program Coordinator – Welcoming the participants

Dr N Venkatesh, Asst. Professor – delivering his lecture on Phytosomes

Dr K Gowthamarajan, Professor & Head- Delivering his lecture

Demonstration at Herbal Technology Lab

Quality Improvement programme on "Current Scenario: Biopharmaceutical Approach Based Drug Delivery Systems"

Program Schedule - 15-9-2014 to 20-9-2014

Date	Forenoon Session		1 -2 pm	Afternoon session	
	10 am -11. am	11.30 - 1.00 pm		2 pm to 5pm	
15-9-2014	Inaugural Function	Mr. R. Suresh kumar LBDDS(Lipid based drug delivery systems)	L U N C H	**Demo:** Mr. R. Suresh kumar NE/ME-Formulation-Phase diagrams	
16-9-2014	Dr. D. N. Venkatesh Phytosomes –A novel approaches for delivery of phyto constituents	Dr. K. Gowthamarajan Herbal Technology & Regulatory Concerns		**Demo:** Dr. D. Nagasamy Venkatesh Preparation of Phytosomes –A novel approaches for delivery of phyto constituents	
17-9-2014	Dr. K. Gowthamarajan Bio-pharmaceutics approaches in drug delivery system	Dr. V. Senthil Herbal cosmeceuticals their formulation –regulatory Scenario		**Demo:** Dr. K. Gowthamarajan BCP approaches based formulation development	
18-9-2014	Dr. Phani Kumar ANDA Applications	Dr. Ganesh GNK Extrusion & Spheronization		**Demo:** Dr. Ganesh GNK Extrusion & Spheronization	
19-9-2014	Dr. Jawahar. N. Solid Lipid Nanoparticles for Brain delivery	Dr. V. Senthil A Novel target approach for treatment of status epileptics		**Demo:** Dr. Jawahar. N. Formulation of micro emulsion Technique	
20-9-2014	Dr. Nilani Packianathan Patents Designs, Practice & procedure	Dr. Sankar PANOPIC View of IRRs		Dr. R.B. Umamaheshwari Introduction to Intellectual property rights and their economic importance – Academic & Industry perspective	Dr. S.N. Raju Career perceptive
21-9-2014	**Industrial Tour**			**Industrial Tour**	

Note:
Tea breaks: 11. am to 11.30 am & 3.30 pm to 4.00 pm
Department Visit: 11.30 to 12 noon

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JSS College of Pharmacy
Udhagamandalam-643001. The Nilgiris.

Report by

Dr S Ponnusankar
Professor and Head
Dept. of Pharmacy Practice

Submitted to
JSS University
Mysore

OCTOBER 2014

All India Council for Technical Education (AICTE), New Delhi Sponsored
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Short Term Course on
Bio Pharmaceutical Approach Based Drug Delivery Systems and Regulatory Challenges
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Applications of Pharmacokinetics in Clinical Practice
(15th – 27th September 2014)

Organized by:
Department of Pharmacy Practice
JSS College of Pharmacy
Udhagamandalam

Date:
22 - 27th September 2014

Program Sponsored By
All India Council for Technical Education (AICTE)
New Delhi

Venue:
Seminar Hall, JSS College of Pharmacy, Ooty

Report on
All India Council for Technical Education (AICTE), New Delhi sponsored
Quality Improvement Program (QIP)
Short Term Course on
Bio Pharmaceutical Approach Based Drug Delivery Systems and Regulatory Challenges and
Applications of Pharmacokinetics in Clinical Practice

Venue: Seminar Hall, JSS College of Pharmacy, Ooty
Date: 22 - 27th September 2014

Organized By: Dept. of Pharmacy Practice, JSS College of Pharmacy, Ooty

Report submitted by:
Dr S Ponnusankar
Professor & Head / CPE Program Coordinator
Dept. of Pharmacy Practice

22.09.2014 (Day I - Monday)

A week long All India Council for Technical Education (AICTE), New Delhi sponsored Quality Improvement Program (QIP), Short Term Course on Bio Pharmaceutical Approach Based Drug Delivery Systems and Regulatory Challenges and Applications of Pharmacokinetics in Clinical Practice was organized by Dept. of Pharmacy Practice between 22 – 27th September 2014.

Dr S Ponnusankar, Professor & Head, QIP – Program Coordinator welcomed the participants of the QIP and introduced the program to the participants. Further, he also introduced the team members of the QIP program and topics to be covered during the program.

Session - 01

Topic: Orientation to the course / Program
Presenter: Dr KP Arun, Asst. Professor, Dept. of Pharmacy Practice

Dr Arun started his presentation about the orientation of the program and provided information about the applications of pharmacokinetics in clinical situations. Pharmacokinetics is currently defined as the study of the time course of drug absorption, distribution, metabolism, and excretion. Clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.

Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient's drug therapy. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations.

A drug's effect is often related to its concentration at the site of action, so it would be useful to monitor this concentration. Receptor sites of drugs are generally inaccessible to our observations or are widely distributed in the body, and therefore direct measurement of drug concentrations at these sites is not practical. For example, the receptor sites for digoxin are believed to be within the myocardium, and we cannot directly sample drug concentration in this tissue. However, we can measure drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids.

The success of drug therapy is highly dependent on the choice of the drug and drug product and on the design of the dosage regimen. The choice of the drug and drug product, e.g., immediate release versus modified release, is based on the patient's characteristics and the known pharmacokinetics of the drug.
A properly designed dosage regimen tries to achieve a specified concentration of the drug at a receptor site to produce an optimal therapeutic response with minimum adverse effects. Individual variation in pharmacokinetics makes the design of dosage regimens difficult.

Therefore, the application of pharmacokinetics to dosage regimen design must be coordinated with proper clinical evaluation.

Session - 02
Topic: Introduction to Clinical Pharmacokinetics
Presenter: Dr KP Arun, Asst. Professor, Dept. of Pharmacy Practice

Pharmacokinetics is the study of the time course of drug Absorption, Distribution, Metabolism, and Excretion and Clinical Pharmacokinetics is application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in patient(s). A drug’s effect depends on its concentration at the site of action

It is not practicable to measure drug concentration in the receptor sites or tissue. Because, Receptor sites of drugs are generally inaccessible to our observations (e.g.: Digoxin concentration in myocardium) or are widely distributed in the body (e.g.: alpha and beta receptors). The concept of ‘Kinetic Homogeneity’ gives the solution for this. Kinetic Homogeneity describes the predictable relationship between plasma drug concentration and concentration at the receptor site. Changes in the plasma drug concentration reflect proportional changes in drug concentrations at the receptor site, as well as in other tissues. However, few drugs concentrate in some tissues because of physical or chemical properties E.g.: Digoxin, which concentrates in the myocardium and lipid soluble drugs, such as benzodiazepines concentrate in fat. We can also measure drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids

The concept of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics and laid the foundation on which all therapeutic and toxic plasma drug concentrations are established. That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues where the disease process is to be modified by the drug (e.g.:

the central nervous system in Parkinson's disease or bone in osteomyelitis). This assumption, however, may not be true for all drugs.

Pharmacodynamics describes 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. The effect of a drug present at the site of action is determined by that drug's binding with a receptor. Multiple factors are responsible for the therapeutic outcome which results in variation of sensitivity to drug effect from one individual to another.

When the logarithm of concentration is plotted versus effect, we can see that there is a concentration below which no effect is observed and a concentration above which no greater effect is achieved. Therapeutic Range' represents a range of drug concentrations within which the probability of a desired clinical response is relatively high and the probability of unacceptable toxicity is relatively low.

Tolerance may be caused by pharmacokinetic factors (such as increased drug metabolism) or Pharmacodynamic tolerance, which occurs when the same concentration at the receptor site results in a reduced effect with repeated exposure.

In the attempt of explaining complex biological process through simple mathematical models, various assumptions are made regarding the drug movement within the body and accordingly, various compartment models are proposed. Clearance and Volume of distribution are known as primary pharmacokinetic parameters as the former is used for calculating maintenance dose and alter for loading dose calculation.

Session - 03
Topic: Multiple Dosage Regimen
Presenter: Mrs. BS Roopa, Lecturer, Dept. of Pharmacy Practice

Drugs are given in multiple doses to treat chronic disease such as arthritis, hypertension, etc. After single-dose drug administration, the plasma drug level rises above and then falls below the minimum effective concentration (MEC), resulting in a decline in therapeutic effect. To treat chronic disease, multiple-dosage or IV infusion regimens are used to maintain the plasma drug levels within the narrow limits of the therapeutic window (eg: plasma drug concentrations above the MEC but below the minimum toxic concentration or MTC) to achieve optimal clinical effectiveness. These drugs may include antibacterials, cardiotonics, anticonvulsants, hypoglycemics, antihypertensives, hormones, and others. Ideally, a dosage regimen is established for each drug to provide the correct plasma level without excessive fluctuation and drug accumulation outside the therapeutic window.

For certain drugs, such as antibiotics, a desirable MEC can be determined. Some drugs that have a narrow therapeutic range (eg: digoxin and phenytoin) require definition of the therapeutic minimum and maximum nontoxic plasma concentrations (MEC and MTC, respectively). In calculating a multiple-dose regimen, the desired or target plasma drug concentration must be related to a therapeutic

response, and the multiple-dose regimen must be designed to produce plasma concentrations within the therapeutic window.

There are two main parameters that can be adjusted in developing a dosage regimen: (1) the size of the drug dose and (2) τ, the frequency of drug administration (ie, the time interval between doses).

To calculate a multiple-dose regimen for a patient or patients, pharmacokinetic parameters are first obtained from the plasma level–time curve generated by single-dose drug studies. With these pharmacokinetic parameters and knowledge of the size of the dose and dosage interval (τ), the complete plasma level–time curve or the plasma level may be predicted at any time after the beginning of the dosage regimen.

For calculation of multiple-dose regimens, it is necessary to decide whether successive doses of drug will have any effect on the previous dose. The principle of superposition assumes that early doses of drug do not affect the pharmacokinetics of subsequent doses. Therefore, the blood levels after the second, third, or nth dose will overlay or superimpose the blood level attained after the $(n - 1)^{th}$ dose. In addition, the AUC = $(\int_0^{\infty} C_p dt)$ for the first dose is equal to the steady-state area between doses, ie, $(\int_{t_1}^{t_2} C_p dt)$.

Session - 04
Topic: Concept of Organ Clearance
Presenter: Dr GK Sadagoban, Lecturer, Dept. of Pharmacy Practice

Organ clearance reflects the ability of the eliminating organ to remove a drug from the blood and also explained pharmacokinetically more meaningful interpretation of organ clearance. Organ clearance can also be viewed as a proportionality constant relating the elimination rate of a drug from blood by the organ to the drug concentration in blood per fusing through the organ.

Extraction Efficiency represents the fraction of the amount (or concentration) of drug entering the organ that is extracted by the organ during perfusion.

E value and its significance: E is dimensionless and ranges between 0 and 1 (sometimes expressed as a percent). E = 0 means that the organ does not remove drug at all during perfusion, whereas E = 1 indicates the complete elimination of a drug from the blood by the organ during perfusion. When E is greater than 0.7, between 0.3 and 0.7 or smaller than 0.3, organ clearance is considered to be high, moderate, or low, respectively. Availability of a drug after it passes through the eliminating organ can be expressed as 1 – E

Hepatic Clearance implies clearance via both metabolism and biliary excretion. Hepatocytes, the principal cell type in the liver, contain various metabolizing enzymes such as cytochrome P450 and

uridine diphosphate glucuronyl transferase (UDPGT) .These are well equipped with active transporters for efficient uptake of drug and excretion into the bile. Several pharmacokinetic models have been developed to enable estimates of organ clearance. The most well-known hepatic clearance models include “well-stirred (or venous equilibrium),” “parallel-tube (or sinusoidal perfusion),” and “dispersion” models.

Well-stirred (or venous equilibrium) model views the liver as a single compartment (anatomy of the liver) with a complete mixing of blood. Important assumptions for the well-stirred model
(a) Only unbound drug in blood is subject to elimination (metabolism and/or biliary excretion),
(b) No membrane transport barrier,
(c) No concentration gradient of the drug within the liver,
(d) The concentration of the drug within the liver is equal to that in emergent venous blood,
(e)It follows linear kinetics

Parallel-Tube (Sinusoidal Perfusion) Model views the liver as a group of identical tubes arranged in parallel, with metabolizing enzymes and biliary excretion functions. The parallel-tube model produces a concentration gradient of a drug within the liver along the blood flow path from the portal vein to the hepatic vein regions. Important assumptions for the parallel-tube model are:
(a) Only the drug not bound to blood components is subject to elimination (metabolism and/or biliary excretion),
(b) No membrane transport barrier,
(c) A concentration gradient of the drug within the liver ranged between inlet and outlet drug concentrations and
(d) Linear kinetics.

Hepatic clearance based on the parallel-tube model is The average drug concentration (CLavg) within the liver is Differences between the Well-Stirred and the Parallel-Tube Models

Factors Affecting Hepatic Clearance.
a) Hepatic blood flow rate b) Fraction of a drug not bound to blood components c) Intrinsic hepatic clearance

The most important value of hepatic clearance models is probably their ability to elucidate how the three different factors blood flow, protein binding, and intrinsic clearance that affect hepatic clearance,

Renal Clearance
The renal clearance (Clr) of a drug consists of four different processes glomerular filtration (Cl), active secretion (Clrs), passive reabsorption (Fr), and renal metabolism(C1rm. Clf, Clrs, and Clrm are clearances representing glomerular filtration, active secretion, and renal metabolism. Cl i,s and Qr are intrinsic renal tubular secretion clearance by active transporter(s) and renal blood flow rate, respectively. Fr is the fraction of the drug reabsorbed into the blood from the urine after excretion. GFR is the glomerular filtration rate, at which plasma water is filtered through the glomerulus.

Glomerular Filtration: In the Bowman capsule (glomerulus), drug molecules not bound to blood components are physically filtered through the glomerular capillary because of the renal artery blood pressure. Creatinine (endogenous substance) or inulin can be used to assess GFR because of their negligible protein binding, tubular secretion, and reabsorption.

Active Secretion of a drug occurs mainly at the proximal tubule by transporters located in the tubular membranes. Active secretion clearance is mediated by membrane transporters .Clrs is affected by Qr, fu,b, and Cli,s. Cli,s can be described as Tmax/Km, where Tmax is the maximum capacity of transporter(s) and Km is the apparent Michaelis–Menten constant under linear conditions.

Reabsorption of drug molecules into the renal venous blood occurs mainly at the distal tubule. This process is considered to be passive and diffusional, urinary pH can also play an important role for the reabsorption of weak acidic or basic drugs.

Estimating Renal Clearance: Clr is a proportionality ratio between renal elimination rate of a drug and its concentration in blood. Alternatively, Clr can be estimated by dividing the amount of unchanged drug excreted into the urine over an extended period of time (usually over 24 hr after drug administration in small laboratory animals) by AUC 0–t in blood. The amount of unchanged drug excreted into the urine can be obtained by the urinary drug concentration multiplied by the volume of urine collected, and, in general, AUC 0–t >90% AUC 0- ∞ is desirable for a reliable estimate of Clr.

“Intact nephron hypothesis” is the relationship between creatinine clearance and the functions of the entire nephron.

Creatinine clearance lower than 50 ml/min is indicative of moderate to severe renal failure. These empirical observations suggest that renal impairments do not selectively affect any particular kidney function or cell type, but rather affect the entire nephron.

23.09.2014 (Day II - Tuesday)
Session - 05
Topic: herb-Drug Interactions
Presenter: Dr S Ponnusankar, Professor & Head, Dept. of Pharmacy Practice

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications e.g. herbs traditionally used to decrease glucose concentrations in diabetes could theoretically precipitate hypoglycaemia if taken in combination with conventional drugs. Herbal medicines are ubiquitous: the dearth of reports of adverse events and interactions probably reflects a combination of under-reporting and the benign nature of most herbs used. Due to the increasing use of herbal and other dietary supplements, healthcare providers and consumers need to know whether

problems arise by using these preparations in combination with conventional drugs. The use of herbal products has dramatically increased over the past decade, driving physicians to become educated in regard to potential herbal complications and drug interactions. From 1990 to 1997, the market of herbal product increased by 48%, with 42% of the population using alternative treatments and spending an estimated $27 billion on them. Herbal products are widely available, relatively inexpensive, and often make alluring but unsubstantiated claims. Herbal medicine appeals to consumers who believe that natural herbal products are preferable to synthetic pharmaceuticals. Usually herbal preparations are well thought-out more safe than pharmaceutical drugs although there are some potential adverse reactions from taking both together.

A relevant safety concern associated with the use of herbal medicines is the risk of interaction with prescription medications. This issue is especially important with drugs having narrow therapeutic index such as warfarin or digoxin. Recent examinations have indicated that as many as 16% of prescription drug consumers consume herbal supplements. Exacerbating the problem, herbal remedies are often marketed on the Internet with misleading and unproved claims. Despite repeated warnings, consumers continue to equate ‘‘natural’’ with safe. As use of herbal remedies become more prevalent and reports of adverse effects continue to mount, there arises a need to understand better about potential complications by the healthcare professionals. There are numerous products currently available in the markets that have been associated with toxicity.

The aim of this presentation is to highlight the clinical interactions between herbal remedies and prescribed drugs. Here we present information regarding different approaches used to study the interaction of herbs and drugs that involve drug metabolizing enzymes and transporters. Theoretical herb drug interactions which are based on *in vitro* experiments, animal studies and speculative empirical evidence from clinical studies.

Session - 06
Topic: Drug-Drug Interactions
Presenter: D Raja, Lecturer, Dept. of Pharmacy Practice

The learning objectives of this topic is
1. Identifying the severe / moderate interactions
2. Steps to be followed in identifying interactions
3. Differentiation of speculative and clinically significant interactions
4. Role of a pharmacist in reporting interactions

The expected outcome from completion of this topic is that the participant be able to identify the interactions present in the patient profile. The following titles like scope, incidence, steps in detecting drug interaction, pharmacist role, types, Genetic Polymorphism and Metabolism related interactions are discussed.

Scope of the title: The need for the study and the significance of identifying an interaction with undue speculation was addressed so that the participant can appreciate the importance of differentiating true drug interaction from speculative interaction.

Incidence: The incidence of the interactions were given and the ways for expecting the drug interaction was explained.

Steps in Detecting drug interaction: The steps that to be followed in detecting drug interactions were explained to the participants, then the role of pharmacist in detecting, documenting and reporting the drug interaction were explained in depth to the participants.

The various types of interactions viz pharmacokinetic and pharmacodynamic interactions (based on the mechanism of action) Mild, Moderate and Severe interaction (based on the extent of interactions) were explained to the participants. Importantly the aftermath responsibility of the pharmacist were directed. The genetic concepts which include but not limited to gene, codon, gene expression, polymorphism, single nucleotide polymorphism were all dealt in detail. Also the human categorization based on the CYP P450 metabolism (viz poor metabolizer, rapid metabolizer, ultra rapid metabolizer and wild type) the enzyme inhibition and induction concepts as a result of drug interaction were also discussed.

The topic highly emphasized on the practical approach to identifying drug interactions from the cases based on the concept “where to look” and “when to look”. The participants were given many model patient profile forms and were educated/ demonstrated to identify the drug interaction present in them.

The ways for improving/ developing the drug interaction identification process were also explained in detail to the participant. The template for detecting the drug interaction was provided to the participant for their future use. The drug interaction guide for the Tamilnadu Essential drug list (TNMSC 2013) prepared in house Department of Pharmacy Practice, JSS College of Pharmacy, Ooty was given to them as a model for their future reference.

Session – 07

Topic: BA / BE Principle and protocols

Presenter: Mrs. BS Roopa, Lecturer, Dept. of Pharmacy Practice

Learning Objectives:

- Important Definitions
- Purpose of Conducting BA/BE
- Criteria of preparation of BA/BE protocol
- Methods of assessing BA/BE studies.
- Statistical consideration

Both BA and BE focuses on release of the drug substance from its dosage form and subsequent absorption into systemic circulation. Thus similar approaches of measuring BA should be followed in demonstrating BE.

It is appreciated that PK studies to be conducted during the phases of Clinical Trial of NCEs. But the BA and BE studies to be conducted for the generic drugs.

In vivo studies: BA and BE studies to be performed for oral immediate release formulations. And following criteria to be applied:

- indicated for serious condition requiring assured therapeutic response,
- narrow therapeutic index drugs,
- complicated PK Studies,
- unfavourable physiological properties studies, and
- documented evidence of BA problems.

In vitro studies: Drugs for which applicant provides the following:

- 90% of the administered oral dose is absorbed on mass balance determination or n comparison of intravenous reference dose,
- different strength of drug is manufactured by same manufacturer.

Methods of assessment of BA: Pharmacokinetic indirect method – Plasma data t max, C max, AUC, Urine data Pharmacodynamic method – estimating pharmacological method, Clinical response.

Evaluation of the data: Drug measurement analysis should be accurate, precise & sensitive and Use of more than one analytical method may not be valid. Proper statistical evaluation should be performed on the estimated PK parameters

Design and conduct of the study: Should include, study design, study population, selection criteria, study conditions, sampling methods and schedules, Bio-analytical methods, statistical analysis.

Session - 08

Topic: Population Pharmacokinetics

Presenter: DR KP Arun, Asst. Professor, Dept. of Pharmacy Practice

The popular quote 'ALL HUMANS ARE ALIKE' is true only as a species. Differences exist with respect to age, gender, social habits, etc. including their responsiveness to drugs. The factors determining variations in response to medications include biological factors, cultural factors and environmental factors. Research in the last 40 years has uncovered significant differences among different populations in rates of drug metabolism, clinical responses to drugs and in drug side effects due to genetic variations. To avoid this, substantial dosage adjustments may be necessary, particularly for - drugs of Narrow Therapeutic Index.

USFDA defines 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”. PoP PK overcomes many limitations of traditional PK studies.

A valid assay for the relevant analyte, structural PK model developed from early phase I studies, determined parameters to be observed and suitable protocol for the study are the pre-requisites to conduct Pop PK studies. The sampling designs include, ‘Single pre-dose (or "trough") sampling’, ‘Multiple-trough sampling’ and ‘Full PK screen design / experimental Pop PK design (2-6 samples)’. Full screening can take all kinds of flexible forms such as fixed sampling, random sampling and window sampling.

Non Linear Mixed Effects Modeling (NONMEM)® is a computer program developed by the NONMEM project group at the University of California at San Francisco written in FORTAN 77, designed to fit general statistical (nonlinear) regression type model to data for analyzing population pharmacokinetic data in particular. Proper modeling of these data involves accounting for both unexplainable inter-and intra-subject effects (random effects), as well as measured concomitant effects (fixed effects).

Fixed effects are the known, observable properties of individuals that cause the descriptors (PK Parameters) to vary across the population are called “fixed” effects”. Random effects are “random” in that they can’t be predicted in advance (otherwise, they would become part of the fixed effects). In general, there are two sources of random variability when dealing with biological data viz. “interindividual” / “between-subject” variability (not ‘Noise’ / ‘Error’, It is BIOLOGY) and “intraindividual” / “within-subject” variability (includes ‘Error’ / “noise” in the assay, errors in drug dose, errors in the time of measurement, etc. Let’s say that P is a parameter of a pharmacokinetic model (Cl / V), regardless, the value of P in the ith subject could be related to the typical value of P in the population by the following model: $Pi = PTV + \eta i$, where Pi is the value of the parameter in the i^{th} individual, ηi is the difference between Pi and the value of P for the typical individual, PTV.

The average ηi is NOT very interesting, because it should be 0. However, the variance of η, $\omega 2$ (Omega squared) is very interesting, because it is the variance of P in the population, which is what NONMEM will estimate. Similarly, Variance of ε is $\sigma 2$.

The data for Pop PK analysis should be entered in a specific format in an Excel sheet and to be saved as .csv file. Then this data file is linked in the base program to calculate the population value of PK parameters (viz. CL and Vd, etc.). Then the covariates are introduced one by one to know the impact of such covariate(s) on the PK parameters and decisions are made on the best fit of the data into the model. Such a final model derived can be used clinically in an individual patient to calculate the CL and or Vd of that individual and further dosage adjustment.

24.09.2014 (Day III - Wednesday)

Session - 09

Topic: Bioanalytical Methods – HPLC/ MS

Presenter: Dr S N Meyyanathan, Professor & Head, Dept. of Pharmaceutical Analysis

The development of bioanalytical method(s) is of paramount importance during the process of drug discovery and development, culminating in a marketing approval. The objective of this presentation is to review the sample preparation of drug in biological matrix and to provide practical approaches for determining selectivity, specificity, limit of detection, lower limit of quantitation, linearity, range, accuracy, precision, recovery, stability, ruggedness, and robustness of liquid chromatographic methods to support pharmacokinetic (PK), toxicokinetic, bioavailability, and bioequivalence studies. Bioanalysis, employed for the quantitative determination of drugs and their metabolites in biological fluids, plays a significant role in the evaluation and interpretation of bioequivalence, PK, and toxicokinetic studies. Selective and sensitive analytical methods for quantitative evaluation of drugs and their metabolites are critical for the successful conduct of pre-clinical and/or biopharmaceutics, pharmacokinetics and clinical pharmacology studies.

Practice Session I

Topic: Bioanalytical method development – Demo and Hands on Experience

Demonstration by: Dr S N Meyyanathan, Professor & Head, Dept. of Pharmacy Practice

Practice Session II

Topic: Biostatistics / PK Software – Demo and Practice with problems

Demonstration by: Mr D Raja, Lecturer, Dept. of Pharmacy Practice

25.09.2014 (Day IV - Thursday)

Session - 10

Topic: Altered Pharmacokinetics in Geriatrics

Presenter: Mrs. M. Deepalakshmi, Lecturer, Dept. of Pharmacy Practice

Geriatrics refers to the study of physical – pathophysiological and psychological aspects of the elderly. Geriatrics normally includes individuals of 65 years and above. The statistics have already reported that, the geriatric population has been increasing constantly worldwide due to phenomenal progress in the medical sector. Elderly have multiple disorders and complaints. Cellular mass decreased by about 30% during aging which are irreversible, inevitable and additive leading distinct physiological changes.

Advancing age is characterized by impairment in the function of the many regulatory processes that provide functional integration between cells and organs. Therefore, there may be a failure to maintain homeostasis under conditions of physiological stress. The reduced homeostatic ability affects different regulatory systems in different subjects, thus explaining at least partly the increased interindividual variability occurring as people get older. Important pharmacokinetic and pharmacodynamic changes occur with advancing age. Pharmacokinetic changes include a reduction in renal and hepatic clearance

and an increase in volume of distribution of lipid soluble drugs (hence prolongation of elimination half-life) whereas pharmacodynamic changes involve altered (usually increased) sensitivity to several classes of drugs such as anticoagulants, cardiovascular and psychotropic drugs. This review focuses on the main age-related physiological changes affecting different organ systems and their implications for pharmacokinetics and pharmacodynamics of drugs.

Guidelines for prescribing for elder people

- Appropriate treatment requires adequate clinical assessment and accurate diagnosis
- Problem oriented prescribing i.e., treat only the disorder that need to be treated
- Keep drug regimens simple
- Use low doses and increase slowly
- Avoid polypharmacy
- Consider potential drug interactions
- Provide patients with clear instructions both verbal and in writing
- Review patients and their medications regularly
- If in doubt, don't prescribe

Conclusion

Changes in body composition, hepatic and renal function are responsible for an increase in the volume of distribution of lipid soluble drugs, reduced clearance of lipid soluble and water soluble drugs, respectively. All these changes lead to a prolongation of plasma elimination half-life. Significant pharmacodynamic changes also occur which, in general, tend to increase sensitivity to drugs. The reduced functional reserve itself also leads to an increase in sensitivity by impairing homeostatic compensatory mechanisms. A better understanding of the effects of ageing on the clinical pharmacology of therapeutic agents would enhance the quality of prescribing.

Session - 11

Topic: Altered Pharmacokinetics in Liver Failure

Presenter: Mrs. M. Gomathi, Lecturer, Dept. of Pharmacy Practice

Liver disease can modify the kinetics of drugs biotransformed by the liver. This presentation updated recent developments in this field, with particular emphasis on cytochrome P450 (CYP). CYP is a rapidly expanding area in clinical pharmacology. The information currently available on specific isoforms involved in drug metabolism has increased tremendously over the latest years, but knowledge remains incomplete.

Studies on the effects of liver disease on specific isoenzymes of CYP have shown that some isoforms are more susceptible than others to liver disease. A detailed knowledge of the particular isoenzyme involved in the metabolism of a drug and the impact of liver disease on that enzyme can provide a rational basis for dosage adjustment in patients with hepatic impairment. The capacity of the liver to metabolize drugs depends on hepatic blood flow and liver enzyme activity, both of which can be affected by liver disease. In addition, liver failure can influence the binding of a drug to plasma proteins. These changes can occur

alone or in combination; when they coexist their effect on drug kinetics is synergistic, not simply additive.

The kinetics of drugs with a low hepatic extraction are sensitive to hepatic failure rather than to liver blood flow changes, but drugs having a significant first-pass effect are sensitive to alterations in hepatic blood flow. The following drugs taken as example and discussed are: cardiovascular agents (angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, calcium antagonists, ketanserin, antiarrhythmics and hypolipidaemics), diuretics (torasemide), psychoactive and anticonvulsant agents (benzodiazepines, flumazenil, antidepressants and tiagabine), antiemetics (metoclopramide and serotonin antagonists), antiulcers (acid pump inhibitors), anti-infectives and antiretroviral agents (grepafloxacin, ornidazole, pefloxacin, stavudine and zidovudine), immunosuppressants (cyclosporin and tacrolimus), naltrexone, tolcapone and toremifene.

According to the available data, the kinetics of many drugs are altered by liver disease to an extent that requires dosage adjustment; the problem is to quantify the required changes. Obviously, this requires the evaluation of the degree of hepatic impairment. At present there is no satisfactory test that gives a quantitative measure of liver function and its impairment. A critical evaluation of these methods is provided. Finally, it is important to consider that liver disease not only affects pharmacokinetics but also pharmacodynamics.

Practice Session III

Topic: Biostatistical and Pharmacokinetic Calculation – Hands on Experience
Demonstration by: Dr KP Arun and Dr GK Sadagoban, Dept. of Pharmacy Practice

26.09.2014 (Day V - Friday)

Session - 12

Topic: Individualization of dosage regimen
Presenter: Mrs. M. Deepalakshmi, Lecturer, Dept. of Pharmacy Practice, JSS CP, Ooty

"Adaptation of the dosage regimen in function of the clinical characteristics of the individual, aiming to achieve the best possible therapeutic efficiency at the lowest risk of unwanted effects." The objective of drug therapy is to produce, the desired therapeutic effect, with the highest chance and minimum toxic effects.

The dosage regimen must be first adapted to the patient's characteristics and comorbidities. This initial adaptation realizes a priori individualization. After initiating therapy, the patient's response to the drug must be evaluated and the dosage regimen further adapted in case of ineffective therapy or appearance of undesirable effects. In selected circumstances, the follow-up of an effect marker may improve the monitoring of treatment. Adaptation in response to such feedback information realizes the a posteriori individualization.

The reasons for failure of drug treatment can drive from physiological inter-individual variation of pharmacokinetic parameters, which cannot always be evaluated prior to initiation of drug therapy (e.g.

genetic metabolic differences). Other causes of treatment failure are variation in response due to inter-individual differences in pharmacodynamics (e.g. sensitivity towards the drug), including drug tolerance (diminished pharmacologic responsiveness to the drug). Disease states can further alter the response to drugs, and draw attention to dosage individualization.

Clinical implications: A priori individualization must be considered each time a drug treatment is introduced. After initiating drug therapy, the desired response (e.g. analgesia) and the appearance of undesirable effects (e.g. sleepiness) should be evaluated for each patient. If these features are not satisfactory, an alteration of the dosage regimen should be discussed.

For some drugs, it is standard practice to monitor surrogate markers (e.g. prothrombin time) for evaluating the effectiveness of therapy. For drugs with a narrow therapeutic window having no such effect marker easily followed, regimens can be personalized using Therapeutic Drug Monitoring (TDM).

Session - 13

Topic: Therapeutic Drug Monitoring

Presenter: Dr KP Arun, Asst. Professor, Dept. of Pharmacy Practice

Clinicians routinely monitor drug pharmacodynamics by directly measuring physiological indices of therapeutic response (E.g.: lipid concentration, blood glucose, BP, clotting test). But for many drugs there is no readily available measure of effect or it is insufficiently sensitive. Large interindividual variation between dose and response can make individualizing drug dosage difficult. In other cases it is difficult to distinguish between the progress of the disease and the pharmacological effect of the drug. In these situations 'Therapeutic Drug Monitoring' becomes an essential part of clinical management

Therapeutic drug monitoring, or TDM as it is commonly called, is about using drug serum concentrations, pharmacokinetics, and pharmacodynamics to individualize and optimize patient response to drug therapy. Therapeutic drug monitoring aims to promote optimum drug treatment by maintaining serum drug concentration within a 'Therapeutic Range'.

Therapeutic drug monitoring is a practice applied to a small group of drugs in which there is a direct relationship between concentration and response. Serum concentrations are used as the most practical intermediate endpoint to gauge treatment when there is no clearly observable therapeutic or toxic endpoint. Therapeutic drug monitoring blends knowledge of therapeutics, pharmacology, pharmacokinetics, laboratory technology, and clinical medicine and applies it to certain drugs that require determination of patient specific dosage regimens to maximize therapeutic effectiveness while minimizing toxicity.

TDM will be useful if, the drug in question has a narrow therapeutic range, a direct relationship exists between the drug or drug metabolite levels in plasma and the pharmacological or toxic effects, the therapeutic effect cannot be readily assessed by the clinical observation, large individual variability in steady state plasma concentration exits at any given dose, appropriate analytic techniques are available to determine the drug and metabolite levels.

There should be a valid reason for requesting TDM for a particular drug viz. low therapeutic index, poorly defined clinical end point, etc. The request should contain adequate details about the demography of the patient, drug treatment, sampling time etc. Upon receiving the request, appropriate biological matrix (plasma, serum, whole blood, saliva, etc.) should be selected for measuring the drug concentration. As per the protocol, the biological sample should be collected and analyzed by using a validated bioanalytical method and the results should be communicated as early as possible to the treating physician. Clinical interpretation can 'add value' and convert 'therapeutic measurement service' into 'therapeutic drug monitoring service'. Just relating a drug concentration to a published therapeutic range is not an adequate interpretation. For drugs with linear kinetics the following formula may be used: New Dose = Old Dose x Desired Concentration / Old Concentration. The various reasons for either reduced or enhanced concentration of drug in the biological matrix should be analyzed. The clinician caring for a patient will modify a drug dosage regimen in light of all available information. If the members of the TDM team are well respected, many physicians will accept and implement their recommendations for dosage adjustment, and seek their further advice. Hence, member of the TDM team with appropriate clinical expertise should be available to conduct a successful TDM

Limitations of TDM process include: scientific accuracy of the drug assays, laboratory variability in reporting, limited accessibility and infrastructure facilities, validity of suggested target ranges lack of training and skills and the cost involved.

Session - 14

Topic: Dosage adjustment in children: Pharmacometrics Approach

Presenter: Dr M. Surulivelrajan, Assoc. Professor, Dept. of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, Karnataka

Well Known differences exist between children and adults. Well-designed trials in children are lacking. Dosing schemes are derived from healthy volunteer study data. Extrapolation on the basis of bodyweight in the conventional method is problematic many a times. Ethical, practical and financial constraints of clinical trials in this patient population lead to a situation of scarcity of dedicated studies.

Safety issues have been reported with chloramphenicol, Penicillin and sulphisoxazole when used in children. Population approach uses non-linear mixed effect modelling where PK and PD parameters are simultaneously estimated in all individuals. Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals who represent the target population that ultimately receives relevant doses of drug of interest. Population pharmacokinetic approach helps in resolving variability issues and provides a framework for defining optimum dosing strategies in a population, a subpopulation, or for the individual patient. Population pharmacokinetic approach explain the variability in terms of fixed and random effects and quantify them.

This approach has been effectively used to develop population pharmacokinetic models to drugs like Amikacin, lamotrigine, methotrexate. These models have been effectively used to individualize dosage regimen for these drugs in children.

It has been proposed on the use of population PK–PD modeling and simulation to develop evidence-based dosing schemes for children. This approach will allow for sparse sampling in children and reduce the burden for the individual child. Clinical pharmacists have good potential for learning and implementing this approach in their practice because of their knowledge in multiple domains.

Session - 15

Topic: Impact of genetic polymorphism on Anti-Epileptics Drug (AEDs) therapy in clinical practice
Presenter: Dr. Kesavan, Asst. Professor, Dept. of Pharmacology, JIPMER, Pondicherry

Pharmacogenetics (PG) deals with how variations in a gene's DNA sequence can lead to differential drug efficacy and safety. If a gene encoding a drug metabolism protein is mutated, it leads to reduced enzymatic activity. Hence, the patient may have trouble in metabolizing the drug and excreting it out of the body. These individuals are known as poor metabolizers (PMs). A patient who is a PM is at increased risk for experiencing an adverse drug reaction, as the plasma concentrated of the drug could be too high and toxic for the patient. Hence, the dose need to be tailored according to the metabolizing status of the individuals that can be identified with help of Pharmacogenetics studies.

Currently, Pharmacogenetics studies focus more on genes encoding drug transporters, drug metabolizing enzymes and drug targets. Among this, polymorphism of drug metabolizing enzymes has the greatest effect on inter-individual variability of drug response, as demonstrated by many studies. These polymorphisms affect the response of individuals to drugs used in the treatment of cancer, cardiovascular disorders, depression, epilepsy, psychosis, ulcer and gastrointestinal disorders, pain etc. The presentation was focused on the challenges in epilepsy treatment. Anti-epileptic drug response or toxicities are all multifactorially determined, i.e., influenced by interactions of multiple genetic, environmental, disease-related, and drug-related factors.

Identifying factors that predict Anti-epileptic drug (AEDs) response in terms of efficacy and/or ADRs will shift the current practice of trial and error in the treatment of epilepsy towards a more targeted, more efficacious, and less harmful treatment. These objectives could be possible with the help of pharmacogenetics studies which identify the inherited basis of inter-individual differences in the drug response. The tailoring of anti-epileptic drug dose with help of pharmacogenetics studies was explained to the participants. The impact of genetic polymorphism on phenytoin induced neurological toxicities, carbamazepine induced severe cutaneous adverse reactions were discussed in detail in relevance to Indian population. Further, gene-nutritional interaction was also explained to the participants.

27.09.2014 (Day VI - Saturday)

Session – 16

Topic: *In vitro* and *in vivo* assessment of herb-drug interactions
Presenter: Dr S Ponnusankar, professor & Head, Dept. of Pharmacy Practice

Herbal products contain several chemicals that are metabolized by phase 1 and phase 2 pathways and also serve as substrates for certain transporters. Due to their interaction with these enzymes and

transporters there is a potential for alteration in the activity of drug metabolizing enzymes and transporters in presence of herbal components.

Cytochrome P450 induction and inhibition of drug metabolizing enzymes and transporters by herbal component has been documented in several *in vitro* studies. While these studies offer a system to determine the potential for herbal component to alter the pharmacokinetics of a drug, they cannot always be used to predict the magnitude of any potential effect *in vivo*. *In vivo* studies are the ultimate way to determine the clinical importance of herb drug interactions. However, lack of content uniformity and lack of documentation of the bioavailability of herbal components makes even *in vivo* human studies difficult to interpret as the effect may be product specific. It appears that St. John's wort extract is probably one of the most important herbal product that increases the metabolism and decreases the efficacy of several drugs. Milk thistle on the other hand appears to have minimal effect on phase 1 pathways and limited data exists for phase 2 pathways and transporter activity *in vivo*. Further systematic studies are necessary to assess the significance of herb drug interactions.

Practice Session IV

Topic: Pharmacokinetic Calculation – Hands on Experience
Demonstration by: Dr KP Arun, Dept. of Pharmacy Practice

Valedictory Function

Dr S Ponnusankar, Prof & Head, Dept. of Pharmacy Practice and QIP Program Coordinator thanked all the participants and speakers for actively participating in the program and their valuable contribution for the successful completion of the program. Participants shared their learning and stay experiences with the staff and coordinator. Feedback was obtained from the participants to further enhance our program experiences. Participation certificate was distributed to all the participants.

I take this opportunity to thank Principal, JSS College of Pharmacy, Ooty and the JSS University, Mysore for providing permission to organize this one week QIP Short Term Course on Applications of Pharmacokinetics in Clinical Pharmacy Practice at our department. I also thank all India Council for Pharmaceutical Education (AICTE), New Delhi for supporting our program through sponsorship.

Dr. S. Ponnusankar
QIP Program Coordinator
Prof & Head, Dept. of Pharmacy Practice

JSS University, Mysore

JSS COLLEGE OF PHARMACY, OOTY

Quality Improvement Programme (QIP)

on

Biopharmaceutical Approach Based Drug Delivery Systems and Regulatory Challenges

&

Applications of Pharmacokinetics in Clinical Pharmacy Practice

(15th - 27th September, 2014)

Program Schedule of QIP – Week 2

Date / Day	Session I	Session II		Session III	Session IV
22.09.2014 Monday	Orientation to the course / program	Introduction to clinical pharmacokinetics		Multiple Dosage Regimen	Concept of Organ Clearance
23.09.2014 Tuesday	Drug – Herb Interactions	Drug – Drug Interactions		BA/ BE – Principle and Protocols	Population Pharmacokinetics
24.09.2014 Wednesday	Bioanalytical Methods HPLC/ LC-MS	Bio-analytical method development – Demo and Hands on Experience		Biostatistics / PK Software Demo & Practice Problems	
25.09.2014 Thursday	Altered Pharmacokinetics in Geriatrics	Altered PK in Liver failure	**L U N C H**	Biostatistical and PK Calculation – Hands-On-Experience	
26.09.2014 Friday	Individualization of dosage regimen	Therapeutic Drug Monitoring		Dosage adjustment in children: Pharmacometrics Approach	Impact of genetic polymorphism on Anti-Epileptics Drug (AEDs) therapy in clinical practice
27.09.2014 Saturday	*In vitro* and *in vivo* assessment of herb-drug interactions	Pharmacokinetics – Calculation Hands-On-Experience		Pharmacokinetics – Calculation Hands-On-Experience	Feedback and Panel Discussion & Valedictory Function