1. INTRODUCTION
"Inter-individual variations of drugs pharmacokinetic parameters, resulting in fairly different plasma concentration-time profiles after administration of the same dose to different patients." Substantial differences in response to most drugs exist among patients. Therefore, the therapeutic standard dose of a drug, which is based on trials in healthy volunteers and patients, is not suitable for every patient. Variability exists in both pharmacokinetics and pharmacodynamics. For a typical drug, one standard deviation in the values observed for bioavailability (F), clearance (CL) and volume of distribution (Vd) would be about 20%, 50% and 30% respectively. Therefore, 95% of the time, the average concentration (Cav) will be between 35% and 270% of the target value. The most important factors in variability of pharmacokinetic parameters are: Genetic, Disease, Age and body size, Concomitant drugs, Environmental factors (e.g. foods, pollutants) and other factors include compliance, pregnancy, alcohol intake, seasonal variations, gender, or conditions of drug intake.

1.1. Genetic
Patients vary widely in their responses to drugs. Important factors in variability are drug metabolism and drug transport. Inter-individual variation of drug metabolism is due to several factors. Genetic polymorphism is one of them and is defined by the presence, in a normal population, of monogenic traits that exist in at least two phenotypes, neither of which is rare (less than 1%). Genetic variability has been historically illustrated by the metabolism of isoniazid. Isoniazid is primarily acetylated in the liver to N-acetylisoniazid, a precursor of a hepatotoxic compound. Large genetically controlled ethnic differences exist in the distribution of acetylator status (slow and rapid acetylators). Adverse effects may occur prevalently in slow acetylators. On the other hand, rapid acetylators may be more susceptible to adverse reactions such as isoniazid-induced hepatic damage. Later on, it has been found that the majority of metabolic polymorphisms involve the isoenzymes of the cytochrome P450 system.

1.2. Diseases
Concurrent diseases affecting the patient, including the one for which the drug is used, can modify drug response. As discussed below, diseases of the organs of elimination, e.g. the liver and the kidneys, are responsible for large variations in drug pharmacokinetics. Circulatory disorders are also important in pharmacokinetic variability. Diminished vascular perfusion of one or more parts of the body is encountered in conditions such as cardiac failure. This diminished perfusion can affect the different pharmacokinetic mechanisms: 1. perfusion of the absorption sites influences absorption, 2. variation of body perfusion may alter the drug distribution to certain organs, and 3. perfusion of the liver and kidneys affect the metabolism and excretion of the drug. Drugs that are largely metabolized in the liver are affected by liver diseases such as cirrhosis. Biliary excretion may be altered by conditions such as obstructive jaundice. It is worthwhile to remind that hepatic disorders affect not only the metabolism and excretion of drugs but also their absorption (through first-pass effect) and distribution (through protein binding). In conditions such as cirrhosis, oral bioavailability of drugs undergoing a substantial hepatic first pass effect can be greatly increased. In patients with hepatic impairment, there is a decrease in plasma protein synthesis by the liver. This decrease may affect the volume of distribution of drugs that are extensively bound to these proteins. In patients with a compromised renal function, urinary excretion of drugs is diminished. Therefore, the clearance of many drugs is also reduced. In first approximation, this reduction is proportional to the decrease in renal function. Notice that renal diseases may also affect the pharmacokinetics of drugs eliminated through metabolism. For example, insufficient excretion of metabolites can induce toxicity. Also, uremia decreases the liver enzyomatic activity and displaces drugs from plasma proteins.

1.3. Age
Aging is an additional source of variability in drug pharmacokinetics. This age-induced variability is considered for each of the four main pharmacokinetic mechanisms:

1. Absorption: Drug absorption does not appear to change dramatically with age. Generally, changes in the rate rather than in the extent of absorption are found. As exceptions, marked differences in absorption are observed in the neonatal period and in the elderly. In both cases, a decrease in hepatic metabolism and first pass effect may lead to an increase in oral bioavailability of some drugs.

2. Distribution: The volume of distribution is frequently directly proportional to body weight and modulated by age. In some cases, age-related changes in drug binding can affect the volume of distribution (e.g. decrease in extracellular fluid in the elderly).

3. Metabolism: Aging clearly affects metabolism. The enzymes involved in both phase I and phase II metabolism mature gradually following the first two to four weeks following postpartum. Full maturity appears in the second decade of life with a subsequent slow decline in function associated with aging. The overall decrease of metabolic clearance is around 1 % per year.

4. Excretion: Renal clearance normalized for bodyweight is depressed in neonates but then rapidly increases to reach a maximum at six months. Throughout adulthood, age is associated with an average decrease in renal function of 1% per year. But most strikingly, age is associated to an increase in the variability of renal clearance among individuals.
Concomitant drugs

In many patients, several drugs are given concomitantly in order to increase the treatment efficiency or to treat diseases occurring simultaneously. In such cases, pharmacokinetic interactions between drugs may occur and the therapeutic efficacy or the toxicity of the drugs implied may be affected. Drug interactions may occur during absorption: a drug can influence the rate or the extent of absorption of another drug. For example, metoclopramide hastens gastric emptying therefore accelerating the rate of absorption of certain drugs, e.g. paracetamol. Calcium forms insoluble complexes in the intestinal lumen with tetracycline, therefore decreasing its bioavailability. Erythromycin can dramatically increase the oral bioavailability of midazolam by inhibiting its hepatic first-pass effect. Distribution may also be influenced by drug interactions. Most commonly, a drug that is highly bound to plasma or tissue proteins may be displaced from its binding sites by another drug. In an acute situation, this interaction may be significant if the concentration of the displacer is sufficiently high to occupy most of the protein binding sites. The sites available to bind the displaced drug are thus lowered and the amount of unbound drug, the pharmacologically active moiety, is increased. When the drug and the displacer are given chronically, the unbound concentration of the drug depends on its extraction ratio. For drugs with a low extraction ratio, there is an overall decrease in the total plasma concentration but no change in the unbound drug concentration. On the other hand, for drugs with a high extraction ratio, the total plasma concentration is unchanged but the unbound drug concentration is increased and this may lead to toxicity. Most importantly, elimination may be affected by drug interactions. A drug may inhibit the renal excretion of another drug by competing with its renal tubular transport. Also, drug metabolism may be strongly induced or inhibited by the administration of a concomitant drug. The clearance of the drug is thus modified. Therefore, this type of interaction may easily lead to toxicity or ineffective therapy. Both induction and inhibition can mimic pharmacogenetic influences by phenocopying.

INDORAM AND ITS 6-HYDROXYLATED METABOLITE

inter-subject variation represented the main source of variability in indoramin plasma concentrations with, for example, the between-subjects sum of squares (a measure of the contribution to the total variability) representing 97% of the total sum of squares for Cmax and AUC (0–24). Intra-subject and inter-subject coefficients of variation (C.V.s) were circa 20% and 100% respectively for both these parameters. Variability in 6-hydroxyindoramin concentrations was much lower and was approximately equally distributed from intra- and inter-subject variation, with the C.V.s being approximately 44% for both Cmax and AUC (0–24).

NIFEDIPINE

Plasma concentrations of Nifedipine were measured following single oral doses of Nifedipine Slow Release (Adalat Retard) on three separate occasions to young, healthy volunteers of both sexes. Intra- and inter-subject variability was assessed by comparing the pharmacokinetic parameters, AUC, $C_{\text{max}}$ and $T_{\text{max}}$. Interindividual variability was less than that observed in other studies with the betablockers, metoprolol and propranolol and there was no evidence of differences between the sexes.

RISEDONATE

Risedronate after single-dose oral administration of 30 mg risedronate as a tablet and an aqueous solution, and 0.3 mg risedronate as an intravenous infusion. This study was a randomized, three-treatment, four-period, partial replicate crossover study involving 33 healthy volunteers. Treatments were administered 7 weeks apart, and the third treatment was repeated during the fourth period. Serum and urine were collected over 72 hours and 672 hours, respectively. Following intravenous administration, renal clearance accounted for 87% of total clearance, with 65% of the dose excreted within 24 hours and 85% of the dose excreted within four weeks. The absolute bioavailability was approximately 0.62% after both oral formulations, and the relative bioavailability of orally administered risedronate was 50–80%, and was primarily associated with absorption. The absolute bioavailability of orally administered risedronate is ~0.6%, and is independent of formulation. Variability in the pharmacokinetics following oral administration is primarily associated with intra subject variability in absorption.

RUFLOXACIN

Rufloxacin is a new long-acting, once-daily quinolone antibacterial agent. We evaluated inter- and intra subject variations in pharmacokinetics of rufloxacin following oral administration of 400 mg (two capsules) under controlled conditions, at an interval of 2 weeks (periods I and II), to 12 healthy male subjects. Plasma and urine samples were collected up to 48 h after drug administration. Plasma drug levels determined by bioassay were higher than those measured by high-performance liquid chromatography, indicating that one or more active metabolites were formed. Individual high-performance liquid chromatography plasma rufloxacin concentrations were fitted with a one-compartment open model with first-order input. There were considerable variations in the plasma concentration-time profiles among subjects; for example, the elimination half-life in plasma varied from 14.6 to 95.5 h. However, pharmacokinetic parameters calculated for the two periods did not differ significantly. These results suggest that the intra subject variation in the pharmacokinetics of rufloxacin is usually small in spite of the considerable inter subject variation.

ASPIRIN

Data describing the pharmacokinetics and pharmacodynamics of low dose aspirin (acetylsalicylic acid; ASA) are limited. This single-center study was designed to determine the rate and extent of oral absorption of 80-mg ASA tablets in healthy, young male subjects and to assess the intra- and inter-subject variability of ASA pharmacokinetics and platelet aggregation effects. Ten subjects each received a single, open-label, oral 80-mg ASA dose on three separate days. Each dose was separated by a 2-week washout interval. Blood samples for pharmacokinetic determinations of ASA and its metabolite, salicylic acid (SAA) and platelet aggregation studies were obtained at scheduled time points before and up to 24 hours after each dose. Peak plasma ASA levels of 1 microgram/mL were achieved within 30 minutes. Peak plasma SA levels of approximately 4 micrograms/mL were attained in 1 hour. The terminal half-lives (t1/2) of ASA and SAA were 0.4 and 2.1 hours, respectively. Both ASA and SA pharmacokinetics and the platelet aggregation response to ASA exhibited considerable intra- and inter-subject variability. Inhibition of platelet aggregation was found to relate with ASA area under the plasma concentration versus time curve (AUC).

ITRACONAZOLE

The pharmacokinetics of Itraconazole, an orally effective, broad-spectrum, systemic antifungal agent, was evaluated in five healthy male volunteers. Each subject was studied on days 1 and 15 at the following dosages: 100 mg once daily (regimen A), 200 mg once daily (regimen B), and 200 mg twice daily (regimen C). On each study day, Itraconazole was administered with a standardized meal. Plasma samples were collected for 72 h postdose, and 24-h urine specimens were obtained. On day 1 of regimen C, plasma samples were collected following the second dose. Samples were assayed for Itraconazole by a sensitive, reverse-phase, high-performance liquid chromatography method. Wide intersubject variations in Itraconazole concentration in plasma versus time profiles were observed on all study days. Absorption appeared to be slow, with day 1 mean peak Itraconazole concentrations in plasma of 110 ng/mL at 2.8 h (regimen A), 272 ng/mL at 3.0 h (regimen B), and 553 ng/mL at 3.4 h (regimen C). Mean peak Itraconazole concentrations in plasma on day 15 were 412 ng/mL at 3.0 h (regimen A), 1,070 ng/mL at 4.4 h (regimen B), and 1,980 ng/mL at 6.0 h (regimen C). The steady state was achieved on day 15. The respective elimination half-lives on days 1 and 15 were 15 and 34 h (regimen A), 20.7, and 36.5 h (regimen B), and 25 and 41.7 h (regimen C), respectively. The areas under the plasma concentration versus time curves (0 to infinity) on day 1 were 1,320 (regimen A), 4,160 (regimen B), and 12,600 ng.h/mL (regimen C). With the exception of one patient on day 15 of regimen C, Itraconazole was not detected in the urine. All data support dose-dependent pharmacokinetic behavior for Itraconazole.

DOXEPIN

Balasubramanian et al.
Intra- and Inter-Subject Variation in the Pharmacokinetics of Some Drugs: A Review, Discovery Pharmacy, 2013, 3(7), 3-5, www.discovery.org.in/dp.htm
PHARMACY OF THE MONTH

Commercial preparations of the tricyclic anti-depressant doxepin contain 15% of the more active cis-doxepin and 85% of the trans-isomer. The single dose pharmacokinetics of doxepin and its major metabolite N-desmethyl doxepin were examined in 30 healthy young men. Results for total doxepin showed wide intersubject variation in all pharmacokinetic parameters except tmax and Cmax. Plasma levels of cis-doxepin were extremely low and it was only possible to estimate the stereoselective pharmacokinetics of the parent drug in 3 subjects. The data from those particular subjects resulted in an average ratio of cis- to trans-doxepin isomers in plasma of 15:85. In contrast, the mean plasma levels of cis-N-desmethyl doxepin in 28 subjects exceeded those of the trans-isomer at every time point after 10 h, such that the areas under the plasma concentration versus time curves (AUC) of cis-N-desmethyl doxepin were significantly higher than those of the corresponding trans-isomer. This phenomenon may play an important role in the therapeutic action of doxepin since it has been suggested that cis-N-desmethyl doxepin is pharmacologically active. In 2 subjects, however, the AUC0-inf of trans-N-desmethyl doxepin were respectively 4 and 8 fold higher than those of the cis-isomer.

9. RANITIDINE

Inter- and intra subject variations of ranitidine pharmacokinetics were examined following oral administration of ranitidine tablets (150 mg as base) under controlled conditions at a timed interval of one week (periods I and II) to 12 healthy male subjects. Significant secondary peaks in the plasma concentration-time curves were observed in all subjects in both periods. The first peak occurred at 0.5 to 2.5 h and the second peak at 3 to 6 h after the dosing. There were great variations in the plasma concentration-time profiles among subjects; for example, the area under the plasma concentration-time curve from time 0 to 12 h (AUC0-12) varied from 1905 to 5672 micrograms h/mL. But bioavailability parameters of period I, such as maximum concentration of the first and second plasma peak (Cmax 1 and Cmax 2, respectively), time to first peak (tmax 1), AUC0-12, and AUC from time zero to infinity (AUC0-infinity), were correlated significantly with those of period II. These results suggest that the intra subject variation of ranitidine pharmacokinetics is usually small over at least one week under the controlled conditions of this study, in spite of its great inter subject variation.

10. CHLORPROMAZINE

Interpatient variation in response to therapy with antipsychotic drugs is a major problem. This study was designed to assess the extent of variation in disease-free subjects in whom known sources of variance were controlled as much as possible. The subjects were 32 healthy, nonsmoking males of European origin, aged 18-25 years, and weighing no more than +/- 15% from the ideal weight for height. After an overnight fast, each subject ingested 50 mg of chlorpromazine. Plasma samples were harvested over a 24-hour period during which the subjects were on a standardized, caffeine-free diet. Plasma levels of chlorpromazine were measured by gas-liquid chromatography-mass spectrometry. The results showed wide inter subject variation in all pharmacokinetic parameters including maximum concentration, area under the curve, and oral clearance. Furthermore, none of the data were normally distributed. For each pharmacokinetic parameter, the distribution was leptokurtotic and skewed. As a consequence, the geometric means provided better estimates of central tendency than the arithmetic means. It seems that a major proportion of inter subject variation is an inherent problem that cannot be accounted for by differences in race, diet, smoking habits, or concomitant drug ingestion.

11. HALOPERIDOL

Single oral doses (5 mg) of haloperidol were administered to 36 healthy men (26 black, 10 white) of whom 28 (22 black, 6 white) completed the study. Plasma samples harvested over 96 hours were analyzed for haloperidol and reduced haloperidol by means of a new high performance liquid chromatographic method. Reduced haloperidol was detectable in the plasma of only six of the 28 subjects (five blacks, one white). In these individuals reduced haloperidol plasma concentrations were generally much lower than those of the parent drug. This finding in the present single-dose study is in contrast to literature reports that have described levels of reduced haloperidol higher than those of the parent drug in some patients chronically medicated with haloperidol. There was wide inter subject variation in area under the plasma concentration versus time curve and apparent oral clearance values for haloperidol. The distributions of these pharmacokinetic parameters about their respective means were each leptokurtotic and skewed toward higher values. In each case the geometric mean gave a better estimate of central tendency than the arithmetic mean. Wide inter subject variation prevented the detection of significant differences in these pharmacokinetic parameters between black and white subjects or between smokers and non-smokers.

12. THEOPHYLLINE

A comparative pharmacokinetic study of theophylline between the first and repeated oral administration and the assessment of clinical utility of theophylline test-dose concept were performed in 6 (study I) and 4 (study II) healthy male volunteers with different dosing schedules. In study I, although the average of theophylline systemic clearance (Clsys) was significantly (p less than 0.05) lower in the repeated dosing than in the first dosing, large intersubject variations were observed. Plasma free fatty acids which inhibit drug metabolizing enzyme activity were not influenced by theophylline chronic administration. In study II, the volunteers received oral multiple doses of a theophylline powder preparation to maintain 5 to 15 micrograms/ml plasma concentration on the basis of the pharmacokinetic parameters calculated from the single oral test-dose. A good prediction of the plasma concentration was observed only in one case and the maximum levels in the rest exceeded 20 micrograms/ml, a toxic concentration. Throughout the Studies, a stable Clsys was obtained in smokers, but the Clsys in non-smokers decreased by one third to a half during multiple dosing. These findings suggest that theophylline showed time-dependent pharmacokinetics and that test-dose concept for theophylline may not be applicable in all cases because of a large inter subject variation in the Clsys change between single and multiple dosing.

13. EPIMERIC BUDESONIDE AND FLUTICASONE PROPIONATE

This pharmacokinetic sub study was part of a previously published open-label, randomised, placebo-controlled, 7-period crossover study to evaluate the short-term effects on plasma cortisol levels of inhaled BUD (400, 800, 1600 microg twice daily) and FP (375, 750, 1000 microg twice daily) via pMDI in a group of healthy male volunteers. On the fifth day of each high-dose treatment period (BUD 1600 microg twice daily and FP 1000 microg twice daily), venous blood samples were collected in nine subjects prior to the last dose and at 15 min, 30 min, 1, 2, 4, 6, and 8 h postdose for measurement of plasma drug concentrations to determine the pharmacokinetics of epimeric BUD and FP following inhalation. Both drugs had a rapid absorption half-life (BUD 10 min vs FP 11.3 min), but quite different elimination half-lives (BUD 2.4 h vs FP 7.8 h). Although there were intraindividual differences in the handling of the 22R-and 22S-epimers of BUD, there were no consistent pharmacokinetic differences between the two enantiomers in the group as a whole. Consistent with previous reports of FP’s higher volume of distribution (V) and lower systemic bioavailability (F), the V/F ratio was lower for BUD than FP (498 l vs 8103 l). The parameters with the greatest inter individual variability for both BUD and FP was the rate of systemic absorption from the lung.

Balasubramanian et al. Intra- and Inter-Subject Variation in the Pharmacokinetics of Some Drugs- A Review, Discovery Pharmacy, 2013, 3(7), 3-5, www.discovery.org.in/dp.htm © 2012 discovery publication. All rights reserved