BIOAVAILABILITY, PHARMACOKINETICS AND TOXICOKINETICS IN DRUG DEVELOPMENT

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Introduction

This meeting was organized jointly by Romanian Society of Pharmaceutical Sciences, Romanian Society of Pharmacology, Therapeutics and Clinical Toxicology, Association de Pharmacie Galènique et Industrielle(APGI) and Turkish Association of Pharmaceutical Scientists(TUFTAD). Attendance was around 60 participants from academia and industry. There were invited speakers from Germany, Holland, France, Slovenia, Italy, Switzerland, Greece, Turkey and of course, Romania. The main focus was on bioavailability(BA) and pharmacokinetics(PK).

Bioavailability Issues

Influence of the active ingredient, formulation and in vivo performance were discussed at length by Prof.Dr. Henning Blume(SocraTec, Oberursel, Germany). Drugs like nifedipin exhibit dissolution controlled BA. With such drugs, the dissolution profiles can be correlated to BA profiles. The bioavailability/bioequivalence(BA/BE) behaviour is a quality/efficacy interface of the dosage form. The BA of drugs with poor solubilities can be improved drastically with proper and intelligent formulation. A BA enhancer like palmitoyl carnitin increases cefoxitin absorption. Sucrose enhances the plasma profile of cimetidine, whereas mannitol decreases it. Grapefruit juice and Vitamin E increase the BA of cyclosporin. On the other hand, drugs with high solubilities are candidates for BA/BE waivers.

Influence of physicochemical parameters like partition coefficient, lipophilicity and pKa were stressed by Prof.Dr.Carla Caramella (University of Pavia, Italy). The great majority of new drugs, being highly lipophilic, are poorly water soluble and therefore pose problems of solubilization in aqueous media. So, the old compromise between the need to improve solubility in aqueous environment and to maintain optimal lipophilic character of drugs still exists.

Biopharmaceutical Classification System(BCS) was brought to attention by Prof.Dr.Helga Möller(Zentrallaboratorium Deutscher Apotheker, Eschborn, Germany). It is a system, which considers the effect of permeability, solubility and dissolution on the oral absorption from immediate release products. At the moment, CaCo-2 cells give a good indication of permeability. It is mentioned in FDA SUPAC Guidances and also in EMEA/CPMP draft notes. This issue is also an important consideration in BA waivers.

The importance of assessing the contribution of metabolites in BA/BE studies were brought to consideration by Prof.Dr. Gül Ayanoğlu-Dülger(Marmara University, Istanbul, Turkey). This is especially important, when the parent compound is rapidly metabolized, or when it is not convenient to measure it; and in such cases, where such information would give useful insights in BA/BE issues. However, the importance of determining the parent compound in plasma is not lessened; in fact for the last four months, FDA stopped asking metabolite levels.

Food effects on BA was discussed in length by Prof.Dr. Panos Macheras(School of Pharmacy, Athens, Greece). Five levels of effects are classified(no effect, accelerated, delayed, decreased and increased). The rate limiting processess are: Gastric emptying, dissolution/release, membrane uptake and first pass metabolism. Classical example is the enhancement of absorption of (CYP)3A4 metabolized drugs with grapefruit juice.

Recently, two texts have been released on BA/BE issues: *The FDA Guidance For Industry* and *EMEA Note For Guidance* on BA/BE. These were discussed

at length by Prof.Dr. Stanislav Primozic(Faculty of Pharmacy, Ljubljana, Slovenia). The new approaches suggest the concept of population BE for prescribing the drugs and individual BE for drug substitution. These approaches are to replace the former average BE concept. Although these approaches are yet to be made official, they are nevertheless, open for scientific discussion; in fact, they are the result of accumulated scientific viewpoints in this important area.

Intense problems in dealing with highly variable drugs were discussed by Dr. Barbara Schug(SocraTec,Oberursel, Germany). These drugs exhibit more than 30 % intrasubject variability and from a statistical point of view, require an excessively high number of subjects, which makes such studies unreasonable. An alternative solution might be doing a steady state, multiple dose study, which might dampen the variability. Doing a replicate study might also be helpful.

Dissolution Tests

The critical role of dissolution tests in pharmaceutical development was stressed by Prof.Dr.Philippe Maincent. The physicochemical properties of drug substances, like solubility (in various media), particle size, polymorphism, complexation, hydration state, solvation, etc., are important parameters that characterize the dissolution profile. Dissolution tests are supposed to give an indication of in vitro/in vivo correlations, if that is possible.

Biopharmaceutical Work

An in depth analysis of the physicochemical factors on the surface of "Stealth" corona-core nanoparticles with polyethylene glycol(PEG) chains on the surface was researched by Prof.Dr. Ruxandra Gref(Universite Paris Sud, Paris, France). The plasma protein adsorption onto biodegradable PEG coated polylactic acid(PLA), polylactic co-glycolic acid(PLGA) and poly(e-caprolactone)(PCL) nanoparticles was investigated by gel electrophoresis. The effect of corona PEG thickness and the composition of the core was assessed as regarding competitive protein binding, zeta potential and particle uptake by polymorphonuclear(PMN) cells. Results of these extensive experiments should help in the design of long circulating biodegradable drug carriers.

The effect of pharmaceutical formulation factors was investigated by Prof.Dr. Sorin E. Leucuta(Faculty of Pharmacy, Cluj-Napoca,Romania). The effect of coating on release from propranolol containing sustained release pellets was investigated. The effect of prolonged release nifedipine on pharmacokinetics (PK) and pharmacodynamics (PD) was researched. In vitro release studies were done on oxprenolol loaded bioadhesive microspheres of gelatin/polyacrylic acid(PAA). The release patterns and release kinetics were determined with varying amounts of PAA. In another study, the BA/BE of a test formulation containing ibuprofen was compared with a commercial product. A drug targeting study was carried out with epirubicin-loaded albumin microspheres in rats. In another study, the PK of epirubicin in plasma, lungs, liver, spleen and heart in rats with liposome, nanoparticle and solution type dosage form was investigated.

Pharmacokinetic Issues

Absorption, distribution and disposition are the fundamental processes that determine the pharmacokinetic action. Modelling procedures help us understand the time course of drug profiles in the body and thus gain insight of the drug action under physiological and pathophysiological environment. Therefore it is now easier to design drug dosage regimens for efficacy and safety.

Transfer phenomena in biopharmaceutics and pharmacokinetics was discussed by Assoc.Prof.Dr.Crisan Mircioiu(University of Medicine and Pharmacy "Carol Davila", Bucharest,Romania). The starting point of drug diffusion in pharmaceutical systems start with Fick's laws. These well known differential equations are integrated with appropriate boundary conditions and very important analytical equations result. One very important and useful equation is Higuchi's square root law. However, during applications of such equations, the boundary conditions upon which this law is based, is usually neglected. We need caution in this respect. Another very useful parameter is the partition coefficient. What is usually done, is the eventual employment of some partition coefficient which is dependent on extraction

parameters. This is only an effective parameter, not the basic partition coefficient.

Pharmacokinetic component of drug action mechanism and quantitative structure-activity relationships(QSAR) were discussed by Prof.Dr. Victor A. Voicu and Crisan Mircioiu(University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania). Drug interactions with the receptors play the major role in PD effects. Lipophilicity parameter play an important role in this respect.

The relevance of time concept in PK and interspecies scaling was discussed by Prof.Dr. İlbeyi Ağabeyoğlu(Gazi University, Ankara, Turkey). Relativity concept has brought the relativity of time into serious consideration. Chronological, biological, PK and psychological times are in consideration. From practical allometric approaches, the biological time for animal mammalian species seems to depend on body weight raised to the power 1/4. Physiological and anatomical parameters such as creatinine clearance, organ weights, heart rates, etc. seem to obey such a relationship. From actual calculations, it is seen that PK parameters of mammalian species(especially humans) can be predicted from animal data. Apparently all mammalian species share common PK parameters, as long as appropriate time units are used. These studies brought forward an entirely new family of time scales such as the *kallynochron, apolysichron, dienetichron* and *syndesichron*. An entirely new concept and field is opening before us.