Toxicokinetics-A Review

Merlin, N J; Alfiya, A R; Dharan, Shaiju S . Asian Journal of Pharmacy and Technology ; Raipur Vol. 8, Iss. 3, (Sep 2018).

ABSTRACT (ENGLISH)

For most of the compounds, the single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. [...]repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Application of these techniques give detailed knowledge about the drug kinetics and metabolism; improved assessment strategy with greater efficiency, use fewer animals and provide better data for risk assessment purposes; rescue at-risk programs in preclinical/early clinical development; proactively screen/evaluate leads at early stages using predictive tools for toxicity and mechanism of action; develop preclinical biomarkers of drug response and toxicity; adoption of toxicity management approaches to improve the therapeutic outcomes[6]. The measurement procedures included in the toxicokinetics give multiple doses pharmacokinetic data in the test species, avoidance of duplication of studies of such studies when appropriate parameters were monitored; optimum design in gathering the data will reduce the number ofanimals required (replacement, reduction and refinement{3R}). Toxicokinetic studies is to describe the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study .Increased implementation of toxicokinetic sampling in all stages of toxicity testing could provide significant improvements in terms of efficiency, relevance, reliability, time constrains and budget.

FULL TEXT

Merlin. N. J*, Alfiya. A. R, Shaiju S Dharan
Department of Pharmacology Ezhuthachan College of Pharmaceutical Sciences Marayamuttom Trivandrum

*Corresponding Author E-mail: merlinbinu76@yahoo.co.in

ABSTRACT:
Toxicokinetics (TK) is 'the generation of pharmacokinetic data, either as an integral component in the conduct of non-clinical toxicity studies or in specially designed supportive studies, to assess systemic exposure. Physiologically based toxicokinetic [(PBTK), or alternatively referred to as physiologically based pharmacokinetic (PBPK)] models are quantitative descriptions of absorption, distribution, metabolism, and excretion of chemicals. Toxicokinetics, toxicodynamics and toxicogenomics (TK/TD/TG) methods are the potential tools in human health risk assessment.

KEYWORDS: Toxicokinetics, PBTK model, PBPK model, safety assessment, Drug development

INTRODUCTION:
Toxicokinetics is defined as the description of the concentration of a compound in plasma (or serum or whole blood) with respect to time, based on a limited number of plasma samples, as a measure for internal exposure within a toxicity study. It is the general framework in which during toxicity testing kinetics is studied in order to assess systemic exposure within toxicity studies. Also toxicokinetics is defined as the study of the time course of xenobiotic absorption, distribution, metabolism and excretion [1]. Toxicokinetics is a composite term for the characterization of the exposure of a test animal to a drug or chemical at doses which elicit a toxic response. Typically, toxicokinetic data are obtained by analysis of blood or plasma samples taken sequentially from test

animals during the course of exposure to different dosages of a drug or chemicals.
Knowledge of toxicokinetics is for evaluating toxicity or for selecting dosages to be administered to animals in toxicology studies [2]. A goal of most toxicity research is to infer expected human health risks from the results in test animals. Animals are commonly exposed to extremely high concentration of test chemicals, by unusual routes of administration, for their entire life time. The challenge is to extrapolate from animal results to predict effects in human population that have very different exposure patterns [3].
Toxicokinetics involves the generation of kinetic data to assess systemic exposure, either as an integral component of preclinical toxicity studies, or in specially designed supportive studies. These data help to understand the relationship between observed toxicity and administered dose. They also play a role in the clinical setting, assisting in the setting of plasma limits for early human exposure and in the calculation of safety margins [4].

TOXICOKINETIC MODELS:

Toxicokinetics describes by means of mathematical functions, i.e. the time-and dose-dependent processes of absorption, distribution, metabolism, and excretion of a substance in animals and humans. Toxicokinetic models are used, mostly straightforward compartment models by physiological toxicokinetic models to predict species-specifically the substance burdens in various tissues and organs. Toxicokinetic information is required for the quantitative assessment of the substance-specific health risk carried out by national and international agencies responsible for regulating health and safety [3].
Physiologically based toxicokinetic [(PBTK), or alternatively referred to as physiologically based pharmacokinetic (PBPK)] models are quantitative descriptions of absorption, distribution, metabolism, and excretion of chemicals. PBTK model is an effective tool for designing toxicology experiments and for conducting extrapolations essential for risk assessments [5]. Validated PBPK models permit calculation of tissue doses of xenobiotics and metabolites for a variety of conditions, i.e. at low-doses, in different animal species, and in different members of a human population. PBPK models givessupport to low-dose and interspecies extrapolations that are important components of current risk assessment methodologies. PBPK models are sometimes referred to as physiological toxicokinetic (PT) models to emphasize their application with compounds causing toxic responses [6].
Pharmacokinetic (PK) models have the potential to estimate time course concentrations of parent compounds and metabolites for different exposure conditions.

Compartment models:

Toxicokinetic evaluation follows the pharmacokinetic models.
In a one-compartment model, there are two important assumptions:
1. Linear pharmacokinetics - elimination is first order and pharmacokinetic parameters (Ke, Vd, Cl) are not affected by the amount of the dose i.e. a change in dose is proportional to change in plasma concentration.
2. Immediate distribution and equilibrium of the drug throughout the body. By plotting the graph Cp v/s t profile of a drug after an i.v bolus injection (the same principles apply to other routes of administration as well) by the exponential equation [7]:
Cp (t)=Cp0. e-ket
=Dose/Vd. e-ket
In Cp
In two compartment model, i.v. bolus dose
Comp 1 (central)-blood and well perfused organs, e.g. liver, kidney, etc.
Comp 2 (peripheral)-poorly perfused tissues, e.g. muscle, lean tissue, fat, etc.

TOXICOKINETIC PARAMETERS:

Toxicokinetic (TK) models makes a gap between chemical exposure and measured toxicity endpoints, thereby it gives information about the chemical risk assessments [4]. The risk assessment of potential carcinogens is the determination of toxicokinetic parameters. The partition of the xenobiotic in the body of experimental animals through the formation of DNA adducts which might lead to the development of cancer. Extrapolation from one

species to another can be done by the process of population parameters. The consideration of individual parameters varying between repeated experiments and different doses is of great importance to obtain a more precise insight into the variability structure of the process so that a valid basis for further research is the final result. The estimation of the individual and population parameters is performed by an EM algorithm [5].
Toxicokinetic assessments can be conducted in parallel or concurrent with ongoing toxicology programs and in compliance with GLP requirements.The following are the toxicokinetic parameters.
Cmax-Maximum concentration of compound observed in the matrix of interest.
Tmax-Time of maximum concentration.
(lambda)-Terminal elimination rate constant (slope from a semi-log concentration vs time plot).
t 1/2(half-life)-The time it takes for the concentration of the compound to decrease by 50%. Half-life is a secondary pharmacokinetic parameter which is determined by the volume of distribution (V) and clearance (Cl) of the compound.
AUC-Area under the concentration vs time curve.
AUMC- Area under the first statistical moment curve.
Vd-Volume of distribution
Cl (Clearance)-Volume of fluid (usually blood) from which compound is removed completely per unit time.
Mathematically:
Cl=Dose/AUC
MRT-Mean Residence Time (MRT)-The average time one molecule resides in the body
MRT=AUMC/AUC
MAT-Mean absorption time
F-Bioavailability factor
t-Time.

In Vivo PK Studies

Rank-ordering compounds/formulations

The rank-ordering method was designed for the purpose of mapping a known cut-score (e.g. a grade boundary mark) on one test to an equivalent point on the mark scale of another test. If the correct mapping were known, then the outcome of a rank-ordering exercise could be compared against that. The validation of this method in terms of its rationale, its psychological validity, and the stability of the outcome when various factors incidental to the method are varied (e.g. methods of data modelling and analysis).

Bioavailability and bioequivalence:

Bioavailability is defined as the rate and the absorption of drug that reaches the biological system in an active form, capable of exerting the desired pharmacological effect, including its onset, intensity and duration of its action. The bioequivalence is said to exist when the bioavailability of a drug with different formulation is same.

Dose proportionality (ascending dose) and dose linearity (multiple dose):

Dose linearity and dose proportionality are usually tested. It is essential to determine whether the dispositions of a new drug are linear or nonlinear. Drugs which behave non-linearly are difficult to use in clinics, especially if the therapeutic window is narrow. If non-linearity is observed for the usual therapeutic concentration range, more clinical studies/tests are needed for the drug development program and drug development can even be stopped.

Drug-drug interactions:

In vitro drug-drug interaction studies must be performed with high quality and consistency, particularly when the studies ultimately influence the design of clinical trials. Data obtained in support of drug-drug interaction studies should be collected and documented with the same level of quality applied to other non-GLP (good laboratory practice) preclinical metabolism and pharmacokinetic data.

Tissue distribution (non-radioactive and radioactive):

Tissue distribution studies are an important component in the non-clinical kinetics programme. For most of the compounds, the single dose tissue distribution studies with sufficient sensitivity and specificity will provide an

adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources.

Pharmacodynamic and pharmacokinetic/ pharmacodynamics modeling Pharmacokinetic/ pharmacodynamic (PK/PD)-modeling links dose- concentration relationships (PK) and concentration-effect relationships (PD), thereby facilitating the description and prediction of the time course of drug effects resulting from a certain dosing regimen[8].

APPLICATIONS OF TOXICOKINETICS:

Efficacy and safety of drugs are very important parameters that are evaluated at every stage of drug development and post-marketing. Non-clinical and clinical drug safety evaluation involves assessment of the safety profile of therapeutic agents through the conduct of studies and trials [2].

Toxicokinetics, toxicodynamics and toxicogenomics (TK/TD/TG) methods are the potential tools in human health risk assessment. Application of these techniques give detailed knowledge about the drug kinetics and metabolism; improved assessment strategy with greater efficiency, use fewer animals and provide better data for risk assessment purposes; rescue at-risk programs in preclinical/early clinical development; proactively screen/evaluate leads at early stages using predictive tools for toxicity and mechanism of action; develop preclinical biomarkers of drug response and toxicity; adoption of toxicity management approaches to improve the therapeutic outcomes[6].

Studies reveal the drug toxicity at molecular as well as genetic level that helps researchers and physicians to reduce the undesired effects of drugs. TK/TD/TG approaches are very important to develop experiments designed to understand the molecular basis of drug toxicities [9].

The need for toxicokinetic data and the extent of exposure assessment in individual toxicity studies done in step by step to provide sufficient information for a risk and safety assessment. The measurement procedures included in the toxicokinetics give multiple doses pharmacokinetic data in the test species, avoidance of duplication of studies of such studies when appropriate parameters were monitored; optimum design in gathering the data will reduce the number ofanimals required (replacement, reduction and refinement{3R}). However this toxicokinetic data focus on the kinetics of a new therapeutic agent under the conditions of the toxicity studies themselves [2].

Dynamic development process of a pharmaceutical product is involves continuous feed-back between non-clinical and clinical studies, no detailed recommendations required for the application of toxicokinetic data to be collected in all studies and scientific judgment should dictate when such data may be useful.

Thorough toxicokinetic evaluation is important in drug development stages. This evaluation should constitute effective analytical methods having good accuracy and precision, adequate sampling, drug and metabolites evaluation both in animals and humans and sufficient results evaluation [10].

Toxicokinetic data is important to know the toxic responses to that of drug in preclinical which can be used to set safe dose for clinical use of new drugs. It also gives support to mode of action analysis and extrapolation across exposure routes. Toxicokinetics used in other areas of pharmacokinetics which act as a biomarkers for doing screening studies which provide data for allometric species scaling, measuring drug levels in nonplasma samples (tissues, urine and bile). Even though toxicokinetic evaluation is only a small part of the process of understanding the fate of a drug, it has a vital part in drug development [6].

The evolution of toxicity whether as discrete or sequential, single or multiple events, each effects measured or observed can be identified by toxicokinetic data [9].

The route of administration and the nature of the formulation to be used in humans, as well as the therapeutic indication for which the compound is intended can also be detected.

CONCLUSION:

Toxicokinetic studies is to describe the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study .Increased implementation of toxicokinetic sampling in all stages of toxicity testing could provide significant improvements in terms of efficiency, relevance, reliability, time constrains

and budget.

REFERENCES:

1. Jos GM, Liesbeth G. Proper knowledge on toxicokinetics improves human hazard testing and subsequent health risk characterization. Regulatory Toxicology and pharmacology. 2013; 67:325-334.

2. Gwyn MD, Alan SK, Lewis BK, Colin JF, William DK and Gerald R. The application of toxicokinetic data to dosage selection in toxicology studies. Toxicologic Pathology. 1994; 22 (2):112-123.

3. Melvin EA. Toxicokinetic modeling and its addiction in chemical risk assessment. Toxicology letters. 2003; 138:9-27.

4. Darell D, Sumner JT. Pharmacokinetic Factors Influencing Risk Assessment: Saturation of Biochemical Processes and Cofactor Depletion.1994; 102 (11):13-22.

5. Aude K, Stephanic KB, Sander VL, Elisabeth B. Regulatory assessment of chemical mixtures: Requirements, current approaches and future perspective. Regulatory Toxicology and Pharmacology. 2016; 80:321-334.

6. Krishna MM, Purna CA, Ramya C, Nirmala D, Dheeraj G. Toxicokinetic an important tool in new drug development. International journal of pharmacy and biological sciences. 2011; 1 (3):319-327.

7. Peter GW. Difference between pharmacokinetics and toxicokinetics. Toxicologic pathology. 1995; 23 (2):143-147.

8. Ramsey JC. Nonlinear pharmacokinetics relative to toxicity and use of toxicological data. Drug metabolism Reviews. 2010; 13 (4):779-797.

9. Morgan DG, Kelvin AS, Kiner CB, Kerns WD. The application of toxicokinetic data to dosage selection in toxicology studies. Journal of toxicologic pathology. 2007; 35(6):836-839.

10. Parrott M, Lave T. Application of physiologically based absorption models in drug discovery and development. Journal of Molecular Pharmacology. 2008; 12 (5):760-775.

DETAILS

Subject:	Physiology; Mathematical functions; Population; Pharmacology; Chemicals; Metabolism; Pathology; Toxicology; Animals; Studies; Metabolites; Drug dosages
Publication title:	Asian Journal of Pharmacy and Technology; Raipur
Volume:	8
Issue:	3
Publication year:	2018
Publication date:	Sep 2018

Publisher:	Athena Information Solutions Pvt. Ltd.
Place of publication:	Raipur
Country of publication:	India, Raipur
Publication subject:	Pharmacy And Pharmacology
ISSN:	22315705
e-ISSN:	22315713
Source type:	Scholarly Journals
Language of publication:	English
Document type:	Journal Article
ProQuest document ID:	2286954469
Document URL:	http://search.proquest.com.ezproxy.canterbury.ac.nz/scholarly-journals/toxicokinetics-review/docview/2286954469/se-2?accountid=14499
Copyright:	Copyright 2018 A &V Publication, distributed by Contify.com
Last updated:	2019-09-09
Database:	Health &Medical Collection

LINKS

Search for full text