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TOXICOKINETIC EVALUATION IN PRECLINICAL STUDIES

Nidhi Mishra* and Agrima Srivastava

Amity Institute of Pharmacy, Amity University, Lucknow, Uttar Pradesh.

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***Corresponding Author**
Nidhi Mishra
Amity Institute of Pharmacy,
Amity University, Lucknow,
Uttar Pradesh.

ABSTRACT

Toxicokinetic assessment is both a monitoring or scientific necessity in the drug advancement method. Toxicokinetic is the age of dynamic data to evaluate systemic introduction, either as an essential part of preclinical toxicity studies, or in specifically planned supportive studies. These information help to comprehend the connection between detected toxicity or administered dose. They additionally assume a role in the clinical setting, supporting in the setting of plasma limits for early human introduction and in the estimation of protection limits.

INTRODUCTION

Toxicokinetics TK is study as the application of pharmacokinetics to doses used in testing of toxicology. A (NCE) new chemical entity as part of the safety evaluation target organ toxicity in 2 or 3 animal species, to finding range-finding, acute & pivotal toxicity studies are occur Characterize the target organ toxicity and safety in 3-2animals.These studies in dose employed are many times 10-1000fold increases the used doses to evaluate the preclinical testing in pharmacology of NCEs. Till newly the most pharmacokinetics evaluation of newly, the most pharmacokinetics evaluation of new chemical entity was occur at pharmacological appropriate doses, mostly using various of species or strain of animal to use in safety from dose of pharmacology to extreme doses & the evaluation studies in the safety employed to experimental situation are mostly not meaningful. Thus the necessary to found toxicokinetics programs to occur the specially pharmacokinetics to the greater than doses using in toxicology studies has get easily apparent. The application of (IND) Investigational new drug for the NCEs now daily including toxicokinetics data. These utilised data are to exposure level of support & claims of safety at various dose level.[1]

DEFINITION

Toxicokineticsis deals which study of with absorption, biotransformation, distribution & excretions of chemicals reaction. The explanation of both reactions what rate a chemical will insert the body and what comes to metabolize and excrete the compound directly it is in the body.

PHARMACOKINETICS/TOXICOKINETICS

The study of time course of xenobiotic absorption distribution & metabolism or excretion.

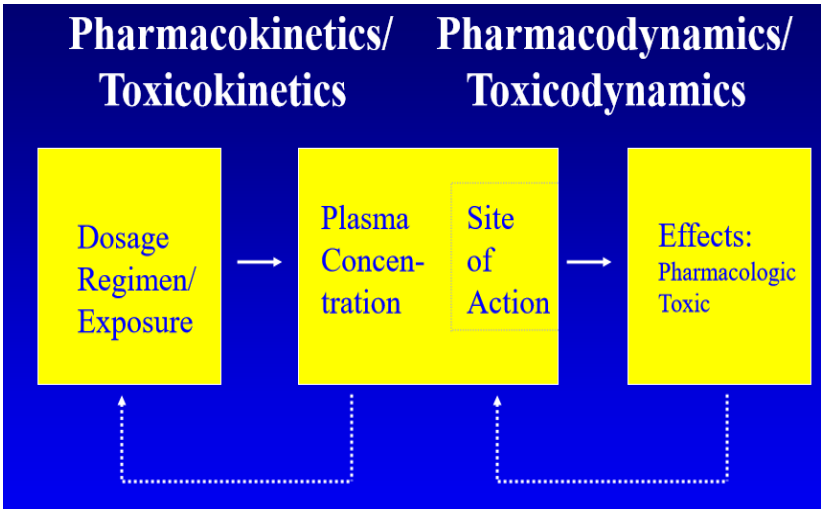


Figure 1: Toxicokinetics.

PRINCIPLE

The application of a toxicokinetics program can be done in a fact which will make easy protocol design and dosing regimen extract and explanation of safety determination by toxicologist outside of compromising the primary target of the study. For example-The blood sample of satisfactory number should be assembled in sequence to measure suitable pharmacokinetics parameters-mainly Tax, Umax, AUC,& T1/2 later oral dosing & also Vdss, CLT later intravenous dosing –without put in change the wellness of the animals & accurate reading in the toxicity of data.[2] The toxicokinetics studies of primary aim –

a-To check sufficient outlook to the NCE in the vital toxicity studies.

b-To measure the time course of this outlook.

c-To measure the connection between the dose and the expanse of absorption of the NCE,

d-To determine the variety in the pharmacokinetics of the NCE upon multiple dosing.

e-To measure a possibility connection between exposure (AUC &Cmax) & toxicity finding.

Terms Used Intoxicokinetics

1-Cmax

A maximum concentration of compound observed in the matrix of interest.

2-**Tmax**

A time of maximum concentration.

Figure 2: Tmax/cmax.

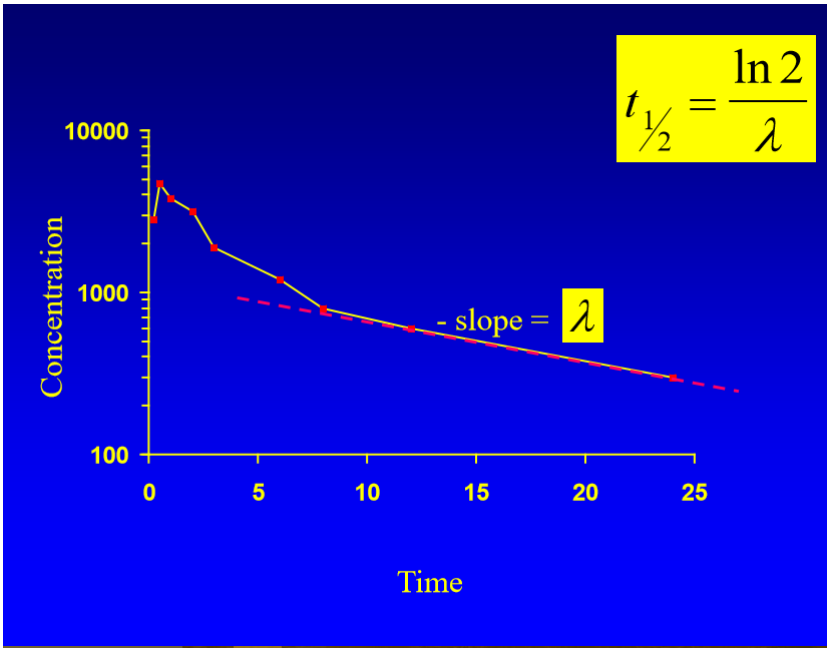
3-Lambda (λ)

A terminal elimination rate constant (slope from a semi-log concentration vs time plot).

4-$T_{1/2}$ half life:

The time it takes for the concentration of the compound to reduce by 50%.A Half-life issecondary pharmacokinetic parameter that is measured by the clearance (CL) & volume of distribution (V) of the compound.

FORMULA= t1/2 =$\frac{O.693 \times V}{CL}$



5-AUC: The area under the concentration vs time curve.

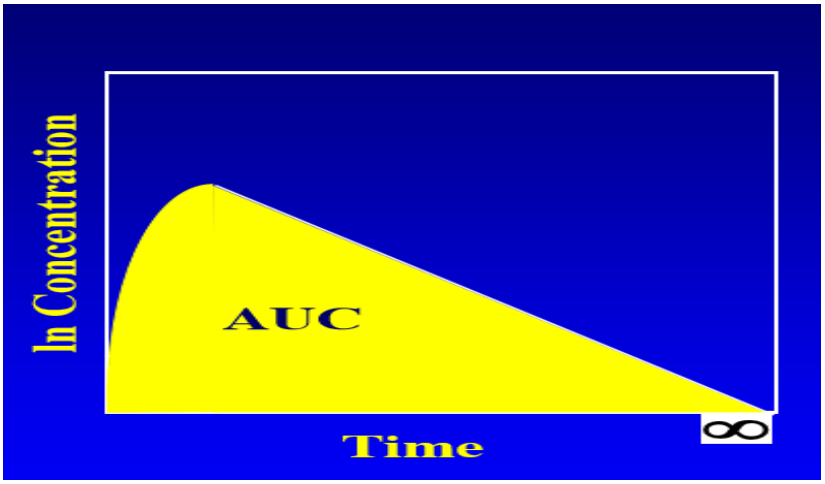


FIGURE 4: AUC.

6-AUMC

The AUMC means area under the first moment curve.

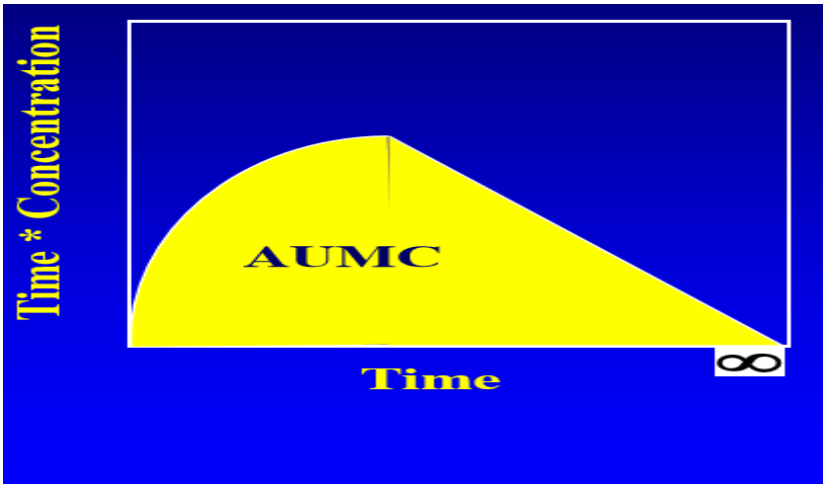


Figure 5: Aumc.

7-Mean Residence Time (MRT)

The average time one molecule resides in the body.

FORMULA

$$MRT = AUMC/AUC$$

8-Clearance (Cl)

The volume of fluid (usually blood) from which compound is removed completely per unit time. BodyOrgans thatmight be elaborate in clearance: **GI tract, Liver, Kidney, Lungs, Other sites (e.g. blood or skin).**

9- Volume of Distribution at Steady-State (Vdss)

A parameter that related plasma concentration to total mass of compound in the body.

10-Fraction Unbound (fu)

A fraction of drug that is not bound to plasma proteins – the unbound concentration is in equilibrium between the tissues and blood.[3]

11-Bioavailability (F)

The fraction of the administered dose that extents the systemic circulation intact.

$$0 < F < 1$$

PRINCIPLE INVOLVED IN TOXICOKINETICS

1. Quantification and Extent Of Exposure

The exposure may be represent by plasma (blood or serum) concentrations or the AUCs of parent metabolites or compound and everytimes by tissue concentrations. Amount of exposure presence a valuation of the load on the experiment species and supports in the explanation of similarly and variance in toxicity across species, dose groups and sexes.

2-Extent of Exposure

The Systemic exposure should be assessed in proper number of animals and dose groups to give a basis for danger assessment. The Associated toxicokinetics may be perform either in all or a demonstrate proportion of the animals species use in the central study or in extraordinary satellite groups.[4]

3. Sampling Points

In concomitant toxicokinetic studies the time points for collecting body fluids should be as common as is essential, but not as everytime as to interfering with the causes undue physiological stress to animal or normally conducted of the study.

4. Dose Level Setting: The toxicity studies of dose level for is mainly regulated by the toxicology outcomes and the test species ofpharmacodynamics responses.

5. Ratifying Factors On Study To Be Considered

The previously discussed species and sex varieties and their effect on toxicokinetics. There are further factors to be measured in this study is tissue uptake, protein binding, metabolic

profile, receptor properties. Systemically exposure may be reduced by tissue uptake and protein binding**.**

6-Route of Administration

The Pharmacokinetics element is significantly affected by the route of administration. For orally administered drugs instant bioavailability duration is further than other routes.

7. Metabolite Determination

The many of cases toxic effect &systemic exposure regard on the origin of parent drug concentration.[5]

8. Statistical Evaluation of Data

The data should be estimated statistically which permits valuation of the exposure. The Toxicokinetic values are generally calculated as mean SD; The usually performed not stastical evaluation however, because large inter & intra-specificvariant of kinetic parameters as follow & numbers of small animals are elaborate in causing toxicokinetic data, a high level of accuracy in statistics is not usually necessary.

9-Analytical Method

A monitoring authorities assumes that analytical methods used to measured plasma concentrations of pharmaceutical are of sufficient sensitivity and accuracy. For estimateauthorized analytical techniques used and follows to (GLP)Good Laboratory Practice. The methods of analytical used in like that studies include gas chromatography (rarely used), & HPLC.

PRECLINICAL STAGE IN TOXICKINETICS STUDIES

1-Assessment of Safety

Mainly a molecule of safety can be achieved in system of in-vivo. This step is not included in the guidelines but most useful for the investigators to measure the molecule of systemic exposure and its effect on it. This study of safety is primary part in thecardio vascular system (CVS), central nervous system (CNS) and respiratory assessments.[6]

2-Studies of Rising & Single Dose

This studies are frequently performed in a very initial phase of development of drug earlier a method of bioanalytical was developed. The mainly performed studies in rodents. The sample

of Plasma may be booked in such studies or put in storage for advanced analysis, if needed; suitablestrength data for the analytic in the matrix sample would then be required.

3- Studies of Repeated –Dose Toxicity

The studies phase-1 give maintain this training is carried out for 4 weeks in both non- rodents as well rodents. The regimen treatment or species would be selected every time possible with regard to pharmacokinetics and pharmacodynamic principles.

4- Studies of Genotoxicity

The studies is essential for both of one IN-Vivo or two In-vitro s support drug of development 14. The investigations of in-vivo mainly use a rodent micronucleus(peripheral erythrocytes or bone marrow) test or chromosome aberration (bone marrow cells) test. This are the well-established studies for the genotoxicity evaluation.

5-Studies of Reproduction Toxicity

The toxicity of reproduction measuring are taken in studies of fertility (rat), Peri- or post-natal growth (rat) &embryo-foetal growth (rabbit / rat).

1- Fertility studies

The fertility toxicity is very important of calculation because the drugs used in mostly in fertility situations so has to strengthen at that time. Mainly this can be performed in rats.

2- Animals in lactating & pregnant

Thetoxic kinetic data in pregnant animals is a regulatory expectation, although no specific supervision is given. The non-pregnant animals data from is useful to limitation of exposure and set dose levels is frequently governed by maternal toxicity.

6-Studies of Carcinogenicity

At times curing purpose drugs are used for long-time, this may lead to the carcinogenicity or toxicity. The studies lifetime in the rodent are compulsory to care the long-term clinical use of pharmaceuticals17 or non-rodents can also be used. The Dose selection is frequently measured as the (MTD) maximum tolerated dose, which is dose –limiting pharmacodynamic effects a 25-fold AUC ratio (rodent to human), or, a maximum feasible dose9, saturation of absorption.

In Clinical Phases Toxicokinetics Studies

The world outlining regulatory bodies on every side is that studies of toxicity are essential to support of human Phase I, II or III studies, and product certificate submission is available3. preclinical level toxicokinetic of estimate for each clinical phase differ sex pressively amongst pharmaceutical companies. The company investigation may simply produce toxicokinetic data from 4-week studies of repeat-dose toxicity. The profile of pharmacokinetics full (including In vitrometabolism studies), and measurements of toxicokinetics from 4 to 13-week studies of repeate dose toxicity prior to necessary is Phase I. Toxicity calculations allow the No Observed adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL) to be recognised for a probable new drug, created on clinical observations, food consumption, clinical pathology, body weight, organ weights, histopathology& necropsy examination. The data of pharmacokinetics from both NOAEL or NOEL [and subsequent toxic level(s)] can be used to provide supervision to the clinical investigator by provided that appropriate safe initial and upper doses in Phase Ithe initial single-dose study. For additional studies of clinical using multiple dosing, data of toxicokinetic from studies of toxicity deliver information on probable drug in plasma of increases or decrease.[7]

TOXICOKINETICS AND PATHOLOGY OF INTERPRETATION DATA IN INTIGRATED FASHION

Toxicokinetics are neccessary in order to interpret accurately the histopathological determine in a toxicological study.

1-In Plasma Exposure Change In Repeated Dose

To explain this hypothetically: Disease changes which did not appear on low doses were marked - after the increase of 2-fold of low dose was seen. If, by compatibility, the plasma exposure is 10 times more likely, then due to a supraproportional increase of plasma exposure, there is the possibility of a vertical dose reaction curve. Increased amounts of plasma exposure with dosage are often seen after the saturation of the clearance pathway (saturation of elimination capacity of the kidneys& liver), or where oral absorption is limited by the efflux transporter at low doses.

Subproporational security of plasma exposure with dose is for example, seen on the upper dose after the active oral absorption or saturation of the solubility boundary. Binding for proteins can be saturated, may be the reason for higher approval at higher doses, because

uninterruptible infarction is available for unconditional kidney or metabolism for filtration clearance.

2-Time Course and Plasma Exposure

For example, compared with a 2 week study, dramatically increased plasma exposure with a 39-week daily dose of conjunction with a consistent performance, in which there was no change, and a relatively small amount of plasma was performed. It is also important to understand the knowledge about plasma exposure for the dose period, whether the dose response relationship has been explained by toxicokinetic.

Toxicity pathologist should be triggered to look at clearing organsliver or kidney more carefully than the increase in plasma exposure on repetitive dose. Exposure to the plasma can be increased with duration of dosage due toeliminate organ and clearance is reduced. Destruction of enzymes involved in metabolism or covalent modification may be less.

The plasma exposure, it can be reduced in repeated instance due to induction (**werboy,** 2001) or a reduction in the concentration of plasma proteins which are leading to Higher fraction about, may been encountered in a toxic study under several conditions.[8]

3- Gender Effect And Plasma Exposure

There are many examples that are specific to a sex. In some of these cases, poisoning incidents play a role. For example: The gender specificity involved in biotransformation is the express enzyme. It is well known that male rodents often have higher expression levels of typical **CYPP450** (Lin et al., 1995; slur et al., 1996). The result of increased.

4-Individual Response And Plasma Exposure

It is of special value for toxic pathologist, to study sensitive animals with "massive" lesions in more detailed description. A holistic view of clinical data, clinical chemistry, toxicokineticsdata and pathology is expressed. A few common causesto be considered is summarized here more closely:

- Check for liver or kidney disease, which can interfere with removal Compound from the body.if available, statistics of individual therapeutic chemistry are very useful for interpretation of study data if related to personal toxicology and pathology.
- Consequences of clinically relevant incidents in the form of vomiting, a dog who was vomiting immediately after oral dosage, May not observed any compounds at all.

- Age of animals: More specifically, non-rodent studies (eg, cynomolgus monkeys) can be used within a study of different age animals, hence the psychological changes related to old age can contribute to abnormal animal of toxicokinetics response (See also discussion about the effects of age time).[9]
- Similarly, due to gastro-intestinal disorder (or uninterrupted diarrhoea), oral absorption can increase or decrease, allowing plasma exposure to be directly affected. In addition to the status of fasting or food, the toxicokinrtics difference may be marked as (Mayor, 1995, Keenan, 1996).

APPLICATION OF TOXICOKINETICS

Application of these some points are include:

1. A scenario of drug kinetics and metabolism more accurate.
2. Improved strategy assessment with more efficiency.
3. The fewer animals used and provide superior data for risk assessment purposes.
4. In preclinical/early clinical development risk programs at rescue.
5. At early stages proactively screen/ evaluate leads using predictive tools for toxicity and mechanism of action.
6. Apre-clinical biomarkers of toxicity & drug response developed.
7. To improve the therapeutic outcomes adoption of toxicity management approaches.
8. The studies of pre-clinical or clinical studies that are focused on research of mechanism of drug toxicity (including kinetics of toxicants) and adverse drug reactions (ADR) using toxicokinetics will be of high interest.
9. The application of toxicokinetics in safety of preclinical drug evaluation and biomarkers identification.
10. The role of toxicokinetics in pharmacokinetics and modified medicine.
11. The toxicokinetics purpose of dosage selection, each toxic expression should be seperately analyzed and a correlation sought between each amount of exposure that best reflects the mechanism of the related toxic effect& pathogenesis.

EXAMPLE

At the point of inflection, limiting toxicity is observed when in the relation is oral doses the AUC reaches a plateau.

Lipophilic compound between free drug of plasma & tissue site of toxicity there is rapid equilibration reversible mode of action.

Biochemically or pharmacological mediated toxicity; primary or secondary mechanism.

In a proportional fashion AUC with dose up to toxic levels of exposure.

In this case, there may be correlation of toxicity either with AUC or plasma concentration at Cmax. Consider in conjunction of the nature and seventy of the toxic effect produced with other endpoints for the purpose of dosage selection should be given equal weight.[10]

CONCLUSION

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 metabolite(s) evaluation both in animals and humans (if necessary) and sufficient results evaluation. Toxicokinetic data is important to know the toxic response(s) to that of drug exposure obtained in drug development stages (preclinical) and it is used to set safe dose for clinical use of new drugs and also it is useful in the understanding of differences in responses or sensitivity between individual animals, genders, species or life stages, and supporting the extrapolation of findings in experimental animals to humans. Kinetic data can also support mode-of action analysis and extrapolation across exposure routes.

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