Preclinical Toxicology - Its Role in New Drug Discovery

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PLENARY LECTURE

Toxicology is the study of the adverse effects of chemical, physical or biological agents on living organisms. It is a multi-disciplinary field that combines various disciplines of biology and chemistry in order to study poisons and their effect on biological systems. Toxicological studies are employed in the field of New Drug Discovery to understand the toxicity of the new drug well enough to make a judgment that it is safe to initiate clinical trials in humans. Principles of toxicology are integral to the proper use of science in risk assessment, where quantitative estimates are made of the potential effects on human health and environmental significance of various types of chemical exposure.

Toxicological evaluations are made in drugs, to determine, if the proposed clinical protocols in man are reasonably safe to initiate, to estimate a "safe" starting dose & parameters for monitoring during phase I clinical trials of new drugs, identify organ(s) toxicities and reversibility, guide dosing regimens and escalation schemes, kinetics and to mimic the duration and intended route of administration in humans. Different type of studies varying from acute, sub acute to chronic exposure of the new drug to at least two different species of animals mimicking the intended route of administration in human, are needed to evaluate the toxicity of a drug. These regulatory toxicity studies are required to be carried out for deciding, on the basis of data from descriptive and mechanistic data, whether a drug or chemical poses a sufficiently low risk to be marketed.

Acute systemic toxicity testing is the estimation of the human hazard potential of a substance by determining its systemic toxicity in a test system (rodents) following an acute exposure. Its assessment

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has traditionally been based on the median lethal dose (LD50) value - an estimate of the dose of a test substance that kills 50% of the test animals. The Globally Harmonized System (GHS), which is implemented in 2008, defines acute toxicity as "those adverse effects occurring following administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.

Sub acute/Sub Chronic toxicity studies predict any cumulative effect of the drug. Compound under test is given daily in 3 dose levels for 2 – 4 weeks (Sub acute), for 90 days (Sub chronic) or more than 90 days (Chronic). Animals are observed for different parameters: physiological, clinical and chemical tests, behaviour, CNS & autonomic profiles. At the end of the test, animals are subjected to the following tests & then are sacrificed. Hematological studies include parameters such as hemoglobin, RBCs, WBCs, platelets etc. Clinical chemistry studies targeting various systems such as liver function, kidney function, general metabolism etc., are carried out from serum or plasma. Histopathological studies for different organs (spinal cord, heart, kidney etc) are also carried out.

In case of toxicity studies that cover the entire life span of the animal (chronic), the same previous procedures are applied but treatment with chemicals starts after weaning of offsprings (litters). Administration of the chemical is continued till death of animals. When animals die spontaneously, the same parameters as mentioned above are determined.

Reproductive toxicity studies are carried out on males and female to identify toxic effects such as decreased libido and impotence, infertility, interrupted pregnancy, (abortion, fetal death, or premature delivery), infant death or childhood morbidity, altered sex ratio and multiple births, chromosome abnormalities and childhood cancer. Developmental Toxicity (toxicity on developing embryo or fetus) helps to identify embryolethality (Failure to conceive, spontaneous abortion), embryotoxicity (Growth retardation or delayed growth of specific organ systems), teratogenicity (Irreversible conditions that leave permanent birth defects in live offspring).

Mutagenic and carcinogenic studies help in evaluating carcinogenicity which, is a complex multistage process of abnormal cell growth and differentiation which can lead to cancer. The initial neoplastic transformation results from the mutation of the cellular genes that control normal cell functions. Mutation may lead to abnormal cell growth. It may involve loss of suppresser genes that usually restrict abnormal cell growth. Many other factors are involved (e.g., growth factors, immune suppression, and hormones).

Safety Pharmacology studies are carried out in animals at the efficacy dose to identify toxic responses of various organ systems. Commonly carried out studies are focused on cardiovascular system, central

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nervous system and respiratory system. Other Safety Pharmacology studies include urinary system, gastrointestinal system and any other systems on a case-by-case basis.

It is the regulatory requirement that all the above mentioned studies are carried out within an internationally acceptable quality system known as Good Laboratory Practice (GLP). GLP is concerned with the organizational process and conditions under which non-clinical toxicity / safety studies are planned, performed, monitored, recorded, reported and archived.

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