CHAPTER-I

TOXICOLOGICAL APPROACHES TO DRUG DISCOVERY

BY:
J. JAYASUTHA
LECTURER
DEPARTMENT OF PHARMACY PRACTICE
SRM COLLEGE OF PHARMACY
SRM UNIVERSITY
• **Animal Toxicology:**

• **Acute toxicity:**

  Acute toxicity studies should be carried out in at least two species, usually mice and rats using the same route as intended for humans.

  In addition, at least two more route should be used to ensure systemic absorption of the drug, this route may depend on the nature of the drug. Mortality should be looked for up to 72 hours after parenteral administration and up to 7 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary.

  LD 50s should be reported preferably with 95 percent confidence limits, if LD 50s cannot be determined, reasons for this should be stated.
• **Long-term toxicity:**

Long-term toxicity studies should be carried out in at least two mammalian species, of which one should be a non-rodent.

The duration of study will depend on whether the application is for marketing permission or for clinical trial, and in the later case, on the phases of trials.

If a species is known to metabolize the drug in the same way as humans, it should be preferred. In long-term toxicity studies, the drug should be administered 7 days a week by the route intended for clinical use in humans. The number of animals required for these studies, i.e., the minimum number on which data should be available.

A control group of animals, given the vehicle alone, should always be included, and three other groups should be given graded doses of the drug; the highest dose should produce observable toxicity, the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans or a multiple of it, for example, 2.5x to make allowance for the sensitivity of the species; the intermediate dose should cause some symptoms, but not gross toxicity or death, and may be placed logarithmically between the other two doses.
• **Reproduction studies:**

  Reproduction studies need to be carried out only if the new drug is proposed to be studied or used in women of childbearing age. Two species should generally be used, one of them being non-rodent if possible.

• **Fertility studies:**

  The drug should be administered to both males and females, beginning a sufficient number of days before mating. In females the medication should be continued after mating and the pregnant one should be treated throughout pregnancy.

  The highest dose used should not affect general health or growth of the animals. The route of administration should be the same as for therapeutic use in humans.

  The control and the treated group should be of similar size and large enough to give at least 20 pregnant animals in the control group of rodents and at least 8 pregnant animals in the control group of non-rodents. Observations should include total examination of the litters from both the groups, including spontaneous abortions, if any.
• **(b) Teratogenicity studies**
  • The drugs should be administered throughout the period of organogenesis, using three dose levels. One of the doses should cause minimum maternal toxicity and one should be the proposed dose for clinical use in humans or multiple of it. The route of administration should be the same as for human therapeutic use.
  
  • The control and the treated groups should consist of at least 20 pregnant females in case of non-rodents, on each dose used. Observations should include the number of implantation sites, restorations if any; and the number foetuses with their sexes, weights and malformations if any.

• **(c) Prenatal studies**
  
  • The drug should be administered throughout the last third of pregnancy and then through lactation and weaning. The control of each treated group should have at least 12 pregnant females and the dose which causes low foetal loss should be continued throughout lactation weaning. Animals should be sacrificed and observations should include macroscopic autopsy and where necessary, histopathology.
• **(d) Local toxicity:**

These studies are required when the new drug is proposed to be used typically in humans. The drug should be applied to an appropriate site to determine local effects in a suitable species such as guinea pigs or rabbits, if the drug is absorbed from the site of applications, appropriate systemic toxicity studies will be required.

• **(e) Mutagenicity and Carcinogenicity:**

These studies are required to be carried out if the drug or its metabolite is related to a known carcinogen or when the nature and action of the drug is such as to suggest a carcinogenic/mutagenic potential. For carcinogenicity studies, at least two species should be used.

These species should not have a high incidence of spontaneous tumours and should preferably be known to metabolize the drug in the same manner as humans.
- At least three dose levels should be used; the highest dose should be sub-lethal but cause observable toxicity; the lowest dose should be comparable to the intended human therapeutic dose or a multiple of it, example 2.5x; to make allowance for the sensitivity of the species; the intermediate dose to be placed logarithmically between the other two doses.

- A control group should always be included. The drug should be administered 7 days a week or a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Observations should include macroscopic changes observed at autopsy and detailed histopathology.