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The importance of toxicity testing

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Abstract

Toxicity testing is paramount in the screening of newly developed drugs before it can be used on humans. The essence of toxicity testing is not just to check how safe a test substance is; but to characterize the possible toxic effects it can produce. The guiding principles of toxicity testing is to check the effect of the test substances on laboratory animals and its direct toxic effect on human and secondly, the exposure of laboratory animals to high doses in order to evaluate its possible hazard on human that are exposed to much lower dose. The present article seeks to highlight the importance of toxicity testing in the development of therapeutic agents. Toxicity testing is of the following types: acute toxicity studies, sub-acute toxicity studies and chronic toxicity studies. Toxicity testing employed wide range of test in different species of animals with long term administration of drug, regular monitoring of physiological, biochemical abnormalities and detailed post mortem examination at the end of the trial to detect gross or histological abnormalities. Toxic effect of drug can range from negligible to severe as to preclude further development of the compound. The use of animal in toxicity testing is most likely to continue for the foreseeable future because of the benefits they offer in examining a whole functioning organism.

Keywords: Laboratory animals, test substance, toxic effect, toxicity testing

INTRODUCTION

Toxicity testing is paramount in the screening of newly developed drugs before it can be used on humans. Toxicity testing is the determination of potential hazards a test substance may likely produced and the characterization of its action, most of the toxicity testing is carried out on experimental animals[1]. The advantages of using animal models in toxicity testing are enormous. These advantages include the possibility of clearly defined genetic constitution and their amenity to controlled exposure, controlled duration of exposure, and the possibility of detailed examination of all tissues following necropsy[1]. The information obtained can serves as the basis for hazard classification and labeling of chemicals in commerce[1]. The essence of toxicity testing is not just to check how safe a test substance is; but to characterize the possible toxic effects it can produce. Toxicity testing was given much attention following early 1960s thalidomide catastrophe; with thousands of children born worldwide with severe birth defects[2]. After this incidence many countries of the world have resolved to go for toxicity testing and teratogenicity in both sexes so as to prevent further tragedies.

Toxicity testing employed wide range of test in different species of animals with long term administration of drug, regular monitoring of physiological, biochemical abnormalities and detailed post mortem examination at the end of the trial to detect gross or histological abnormalities[3]. Dose above therapeutic range are used in toxicity testing to ascertain the toxic signs of action of the drug[2]. The present article seeks to highlight the importance of toxicity testing in the development of therapeutic agents. Toxic effect of drug can range from negligible to severe as to preclude further development of the compound. All toxicity study is supported by; clinical analysis, autophic analysis, haematological and haematochemical analysis, histopathological analysis and statistical presentation and data interpretation.

Importance of toxicity studies

- To establish a dose response curve.
- To ensure safety of new chemicals for use as pesticides, drugs, or food additives before they are registered for general use in industry or doctors clinics.
- To establish the mode of action or mechanism for a toxic effect that may have been seen in other studies.

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- To produce epidemiological studies to explain observations in the population, for instance, the long investigation into the association of smoking with lung
- To validate new methods of testing or investigation, particularly those conducted in vitro rather than in animals[4].

The two basic principles guiding toxicity test in animals

- To check the effect of the test substances on laboratory animals and its direct toxic effect on human.
- Exposure of laboratory animals to high doses in order to evaluate its possible hazard on human that are exposed to much lower doses[3].

Toxicity studies are divided into:

Acute toxicity studies

This is a short term assessment and evaluation of potential hazard test substance or consequences of single dose of a test substance[5]. Acute toxicity testing may be used in risk assessments of chemicals for humans and non-target environmental organisms. Acute toxicity study is better described as LD_{50}, which is defined as the dose which kills 50% of animals. LD_{50} is used for the estimation of the toxicity of the chemical agents. Acute toxicity provides guidelines on the dose to be use in more prolonged studies and it also provides the basis for which other testing program can be design. In acute toxicity studies rodent are mostly used because they are economical and readily available and easy to handle. This test is carried out in each species of animal as the same route as intended to be use in treatment[2].

Importance of acute toxicity testing

- To identify the target organ of toxicity.
- To provides safety measures and monitoring guild lines for workers involved in the development and testing of test substances.
- To provides information needed for the dose selection in prolonged toxicity studies.
- To generate data containing the adverse effects of a substance on human, animal health and environment.
- To provides the basis for which other testing program can be design.
- For academics and regulating purpose; classification, labelling and transportation of chemical agents

Methods employed in acute toxicity evaluation

- Graphical method of Miller and Tainter.
- Arithmetical method of Reed and Muench.
- Arithmetical method of Karbar.
- Lorke's method.

Graphical method of Miller and Tainter

This method is used in the calculation of any ED_{50} values. This involves the administration of same volume of different doses of the test substance to various groups. The animals are divided into five groups of ten animals per group. Group one animals receive the vehicle to which the test substance is dissolved while the other groups are given different doses of the test substance. In this method log doses are plotted on a graph against probits of the percentage[2].

Arithmetical method of Reed and Muench

This method is a cumulative analysis of values obtained from the result of the study. It is generally assumed that the dead of animals would have been caused by the administration of higher dose of the test substance. The cumulative dead and survivors are recorded. The percent of survival is calculated and the LD_{50} is computed[2].

Karber's Method

This method involves the administration of different doses of test substance to various groups which has five animals each. The first group of animals receive the vehicle in which the test substance is dissolved. However, other groups receive different doses of the test substance. The animals in each group receives specific doses, while increment in dose progresses from group to group (starting from group 2 which receives the lowest dose). The interval mean of number of mortality recorded in each group and dose difference across the groups are key parameters in this method. The lethal dose is calculated using the arithmetical method of Karber which is as follows[7].

$$\mathbf{LD_{50} = LD_{100} - \sum ( )}$$

Where LD_{50} = median lethal dose

LD_{100}= least dose required to kill 100%

a= dose differ

b= mean mortality

n= group population

Lorke's method

This test was carried out in two phases.

Phase I

In the first phase, nine mice divided into three groups of three mice each, are given 10, 100, 1000 mg / kg of the test substance. After administration of the test substance, observation is made at regular interval to check for the onset of adverse effect, time to death or time to recover. The period of observation in this phase I is 24 hours.

Phase II

This phase involves the use of three animals divided into three groups. In this phase, the dose level is either step up or down depending on the outcome of the result obtained from phase I. The animals are administered higher dose of 1600, 2900 and 5000 mg/kg. Toxic symptoms are observed for 24 hours as well as delayed toxic symptoms for 7-14 days. The lethal dose is calculated by the formula[6].

LD_{50}= $\mathbf{LD_{50}= \sqrt{(D_0 \times D_{100})}}$

D_0= highest dose that gave no mortality

D_{100}= lowest dose that produced mortality

Sub-acute toxicity studies

This study is conducted to determine organs affected by different dose levels. This study access the nature of toxic dose under more realistic situation than the acute toxicity studies. Three dose levels are normally used[2].

- Dose that is high enough to elicit definite signs of toxicity but not to kill many of the animals.
- Low dose that is expected to induce no toxic effect.
- Intermediate dose.

Doses are generally selected on the basis of information obtained in acute toxicity studies using both LD_{50} and the slope of the dose response curve. The duration of sub-acute toxicity studies depend on intended duration of the test substance[2].

Chronic toxicity studies

This study is basically to determine the organs affected and to check whether the drug is potentially carcinogenic or not. This test extends over a long period of time and it involves large groups of laboratory animals.[5]

Prospect of new test methods and models

Integration of new techniques into existing protocols is definitely going to be a growth area in the future. Genomics, proteomics and metabonomics[4]. The introduction of these new toxicity models provides greater understanding of toxicity in standard laboratory models and also an important factor in the future of toxicity testing. New toxicity model under development include the slug mucosal assay for irritation, transgenic animals, the long-term exposure of hepatocyte cultures and tissue slices and further development of methods for testing for mechanisms of carcinogenicity. The use of invertebrates, as with the slug for the assessment of eye irritation and novel vertebrates such as zebra fish. Stem cells remain the great white hope of toxicity testing; their promise remains just that, at the moment, but may yet blossom[4].

CONCLUSION

Toxicity testing plays a crucial role in ascertaining the toxic effect and characterization of test substance. Toxicity obtained in animal studies occurs with similar incidence and severity in human. The use of animal in toxicity testing is most likely to continue for the foreseeable future because of the benefits they offer in examining a whole functioning organism.

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