Al-Mustaqbal University College
Department of Pharmacy
4th stage
Practical General Toxicology
Lab: 2

Acute Toxicity Study

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Acute Toxicity Studies

- Acute toxicity studies are conducted to evaluate the effects of a **single substance**.
- Usually, each animal receives a **single dose** of the test substance in this study design.
- On rare occasions, **repeated doses** may be administered, but in any event, all doses are administered within **24 h or less**.

Acute Toxicity Studies

Historically, a primary objective of acute toxicity testing was to determine an LD50 dose.

LD 50 is that dose which would be lethal to 50% of the treated animals.

How to get LD50

To achieve this objective, groups of mice, often numbering 10 or more per sex, are treated with a single dose of the test substance.

Depending on the rate of survival in the initial group(s), additional groups are added to the study at higher and/or lower doses.

Most animals that receive the highest doses die and most that receive the lowest doses survive.

How to get LD50

Survival is assessed at some predetermined interval after dosing, usually 7 or 14 days, but occasionally as early as 24 h.

The resultant dose response data can be analyzed by a statistical method.

Informational design

- A more recent design for acute toxicity testing attempts to derive a maximum amount of information from a minimum number of animals.

Informational design

- Study objectives include determination of the most important

1. Clinical signs attributable to high doses of the test substance,
2. Time of onset
3. Remission of those signs

- Possible determination of a minimum lethal dosage, and in the event of lethality, the sequence and timing of effects leading to death or recovery.

Informational design

- These objectives are achieved by means of a comprehensive schedule of animal observations following dosing.
- These objectives can usually be achieved by treating from one to three groups of three to five mice/sex/group at different doses.

Selection of species and route of administration

- **Traditionally, acute toxicity testing of potential new pharmaceutical products is conducted:**

1. **On at least three species, with one being a nonrodent.**
2. **And by at least two routes of administration, one of which is the intended clinical route.**

- **Mice are the most frequently selected rodent species for acute toxicity testing.**

Selection of species and route of administration

- **The choice of routes of administration depends on:**

1. **The intended clinical route**
2. **How much is already known about the oral bioavailability of the test substance.**

Selection of species and route of administration

- If the intended clinical route is oral, acute testing by oral gavage with a solution or suspension is of primary importance.
- If other clinical routes are anticipated (e.g., iv or dermal), they represent good secondary routes for acute testing.

Selection of species and route of administration

- **Ordinarily, at least one parenteral route is used for acute testing, and that route may be**

1. **Intravenous (IV) if the product is soluble in a fairly innocuous vehicle (e.g., water or saline)**
2. **IP as a suspension if the product is insoluble in an aqueous (or other innocuous) vehicle.**

Characteristics of acute toxicity testing

- **There are a few characteristics of acute toxicity testing that are not common in other toxicity protocols.**

1. **To reduce animal use in acute toxicity testing, studies that include more than one dose group are usually dosed sequentially, with an interval of at least 24 h between dosing of subsequent groups.**

Characteristics of acute toxicity testing

2. Another unusual aspect, of acute toxicity studies, is the nutritional status of the animals at dosing. because dosing only occurs on 1day, dietary stress is considered tolerable.
3. The practice of conducting gross necropsies at the end of acute toxicity studies is growing in popularity.

Characteristics of acute toxicity testing

4. The toxicity resulting from acute exposure is usually associated with a biochemical or functional imbalance rather than with a change in the gross or microscopic architecture of an organ system.
5. Microscopic examination of tissue is rarely conducted in acute toxicity studies unless there is some scientific reason to expect it would be useful.

Characteristics of acute toxicity testing

TABLE 2.22 Typical Acute Toxicity Study Design for Mice

Number of mice/sex/dose group	3–5
Number of dose groups	1–3
Number of control groups	None
Dosing frequency	Single dose
Dosing days	I day
Survival checks	Not done (part of Clin. Obs.)
Clinical observations	4 or more on day of treatment, then 1–2 daily
Physical examinations	Not done
Body weights	Prior to dosing
Feed consumption	Not done
Number of reversal mice	None
Duration of reversal period	Not applicable
Blood collection	Not done
Hematology parameters	Not done
Clinical chemistry parameters	Not done
Urine collection	Not done
Necropsy	Gross (increasingly, but rarely useful)
Tissue collection	Rarely (specific cause only)

Benefits of acute toxicity testing

- The results of a well-designed acute toxicity study can help to:

1. Predict likely target organ systems and possible outcome in the event of massive human overexposure.

Benefits of acute toxicity testing

2. **Help in establishing risk categories for EPA classifications**
3. **Help in dose selection for the initial repeated dose toxicity tests to be conducted.**

Thank you for your attention