Finding the Middle Ground

Medicinal drugs have been around for centuries. Throughout the years drugs have been refined to become safer and more effective in their action. However, coming up with a suitable drug is not as simple as it seems.

For a drug to work effectively, it is important that the dose is just right. A dose too small would be ineffective for treatment purposes. On the other hand, a dose too high could have toxic and potentially, lethal effects on an individual.

This is where the median effective and lethal dose come in. They can be used as a parameter in measuring effectiveness and acute toxicity of a drug.¹

The median effective dose is abbreviated to ED₅₀. It is known as the dose required to treat 50% of the test population.²

The median lethal dose is commonly abbreviated to LD₅₀. It is the dose required to cause a lethal effect (mortality) in the 50% of the population.³

How can we determine the ED₅₀ and LD₅₀?

There are several methods that can be used to determine the ED₅₀ and LD₅₀ of a drug. Many of these methods follow similar principles and hence utilise similar steps in their methods.

The way we determine the ED₅₀ and the LD₅₀ may be similar, but the main difference lies in the outcome being achieved. The former seeks the effectiveness of a drug whereas the latter looks for mortality caused by the drug.⁴ Majority of these methods use rats as a test animal. However, it should be noted that the ED₅₀ and LD₅₀ found in an animal will differ by some degree to the ED₅₀ and LD₅₀ of a human due to various factors such as size and blood volume.⁵

Up and Down Method

The up and down method involves using individual animals which are sequentially dosed with a specific drug within a 48-hour interval. Subsequent doses are determined by the result from previous doses. For the determination of the LD₅₀ if the animal survives a certain dose, then the following dose is adjusted upward. If not, then the dose is adjusted downwards in the next test animal. For the determination of the ED₅₀, if there is no effect in the test animal then the next dose is adjusted upwards. If toxic effects are observed, then the dose is
adjusted downwards in the next animal. The adjustment of the doses is determined by a constant factor and testing terminates when the LD₅₀ and ED₅₀ have been determined.⁶

**The Therapeutic Index**

Selecting an effective drug can sometimes be difficult when needing a therapeutic outcome whilst steering clear of any toxic and lethal side effects. That is why we use the therapeutic window which gives an indication of the range a drug would be both effective and safe in. This is quantified by the therapeutic index. The therapeutic index of a drug is there to provide an indication of the level of safety of a drug and compares the effective dose to the lethal dose.⁷

It can be calculated using a simple ratio of the LD₅₀ and ED₅₀:

\[
\frac{LD_{50}}{ED_{50}}
\]

Drugs with a high therapeutic index are preferable to drugs with a low therapeutic index because they require a greater dose to elicit a toxic effect. Whereas a drug with a low therapeutic index would require a much lower dose to elicit a toxic or potentially lethal effect.⁸

**Digoxin**

Digoxin is derived from the foxglove plant *Digitalis lanata*⁹ and is a common drug used to treat heart failure as well as atrial fibrillation.¹⁰ It works by inhibiting the sodium/potassium pump primarily in myocardial cells and allowing for an increase in the intracellular concentration of sodium ions and a reduction in potassium ions. Indirectly it leads to an increase in the intracellular concentration of calcium ions which improves myocardial activity.¹¹

**Limiting Toxicity**

To limit the toxicity of digoxin it is important to administer its dosages within the therapeutic window and monitor its levels in the body. Unfortunately, digoxin toxicity does occur, and treatment is required.

Digoxin has a low therapeutic index hence it can cause toxicity even if given in a small dose. The therapeutic range of Digoxin is 0.5 - 2.1 mg/L which is quite low in comparison to many other drugs.¹² Therefore, it is essential to monitor its’ levels in a patient undergoing digoxin therapy. To limit the chances of toxicity, dosages administered to patients are adjusted according to the patient’s condition and other contributing factors. These can include:

- Age
- Gender
- Disease
- Drug interactions
- Kidney function
- Genetics¹³

Digoxin levels in the body are monitored through its concentrations in the blood serum. The distribution in the body is quite slow thus an accurate serum digoxin concentration reading in the body can’t be made until at least 6 hours after the administration of the drug.¹⁴ However, to ensure that toxicity is avoided through overdosing and that the drug is in the safe range, serum testing is necessary.

**Overcoming Toxicity**

Digoxin toxicity can occur even in the therapeutic range if treatment has been long term or if the patient has a condition that can increase digoxin sensitivity. Such conditions can include: myocardial ischaemia, hypercalcemia and acid-base disturbances in the body. In such cases hospitalisation is required and digoxin-specific antibody fragments may be given to the patient. These bind with digoxin molecules to form a complex that can be excreted out through the urine.¹⁵
References


