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Measuring Acute Toxicity of Indomethacin In Rats Using The Weibull Model

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Abstract

In this paper, the acute toxicity of indomethacin in rats is evaluated by a tolerance distribution model called Weibull model. This is achieved by obtaining the Median Lethal Dose (MLD) for indomethacin. The parameters of the Weibull model are estimated by two popular estimation methods (the maximum likelihood estimation and least square estimation) to obtain the MLD value. The MLD value (a measure of acute toxicity) of indomethacin is obtained as 13.23mg/kg. The implication of the MLD value indicates that indomethacin could be fatal and toxic as a drug if not properly administered.

Keywords: Indomethacin, Weibull model, median lethal dose, acute toxicity, toxicology, tolerance distribution.

1.0 Introduction

On daily basis, we come in contact with chemical substances in form of drugs, food and its additives, pesticides, contaminants, industrial pollutants, etc in our environment. Occasionally, these substances are wrongly prescribed, used and/or abused in such a way that they cause adverse effects to our health. For this reason, there is need to protect humans and other living things from the adverse effects of these chemical substances. This is achieved through scientific studies of chemical substances and their adverse effects on humans, animals and plants. The scientific study of chemicals and observed adverse effects experienced by biological systems is known as toxicology. Literally, toxicology is the study of poison [1]. Toxicology is a multidisciplinary subject which encompasses many areas like chemistry, biology, physics and mathematics. Application of basic biochemical, chemical, pathological, physiological and mathematical knowledge along with experimental observations are to gain an understanding why certain chemicals cause disruption in any biological system, which may lead to adverse or toxic effects. Over the years, many therapeutic medications such as aspirin, paracetamol, indomethacin and other drugs are produced in Nigeria for health benefits. Situations arise when these drugs are abused and the resulting effects could cause unbearable experience, pains or even death. Indomethacin was produced as a therapeutic drug to reduce fever, pain, swelling and/or stiffness in the body. In recent time, it has been used as a popular rodenticide in Nigeria since it kills rats at a fast rate [2]. The origin of its use for this purpose is fairly unknown but report suggests that it all started with the ingestion of the drugs by rats in a pharmacy [3]. Although as a prescription medicine, it is freely sold in Nigerian pharmacies and patent medicine stores without any strict prescription [2]. The use of this drug is causing serious worries among the informed and lay public as to the potentially harmful effects of the drug in humans [2]. For this reason, we shall determine the acute toxicity of indomethacin in rats using the Weibull model (a tolerance distribution model) to ascertain its fatal and toxic nature as well as obtain the MLD.

2.0 Median Lethal Dose (MLD) As A Measure Of Acute Toxicity

In toxicology studies, acute, sub-chronic and reproductive tests are the principal experiments conducted on mammals, birds and some invertebrates in a laboratory. Acute toxicity refers to those adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24hours, or an inhalation exposure of 4 hours. Paracelsus' often cited phrase "all substances are poisons, there is none which is not a poison. The right dose differentiates a

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poison from a remedy" is clearly in reference to acute toxicity [4]. In most acute toxicity tests, a single dose of a test substance is given to the experimental animals to ascertain its potency. One measure of acute toxicity is the median lethal dose (MLD or LD_{50}). MLD value is a measurement useful only as a reference value for classification and labelling purpose. The classification and label criteria for substances are shown in Table 1.

Table 1: Acute toxicity hazard categories and Label elements for acute toxicity

Acute toxicity hazard categories					
Exposure route	**Category 1**	**Category 2**	**Category 3**	**Category 4**	**Category 5**
Oral(mg/kg bodyweight)	0-5	5-50	50-500	500-5000	5000-15000
Hazard statement					
Oral	Supertoxic	Extremely toxic	Very toxic	Moderately toxic	Slightly toxic

Source: [5]

Note: Category 1 indicates highest toxicity while category 5 indicates relatively low toxicity.

3.0 Mathematical Models of Toxicology

Mathematical models are used to analyse adverse effects experienced by test subjects in toxicological studies when doses of a particular chemical substance are administered [6]. Mathematical models used in analyses of dose-response relationship range from very simple models to extremely complicated models for which the eventual functional form cannot be easily expressed as a single equation [6, 7]. Categorically, these models are classified as tolerance distribution, mechanistic, time-to-tumor, biologically-based and physiologically-based pharmacokinetic (PBPK) models [7]. Tolerance distribution models (or statistical models) are models which assume that a population contains individuals of different susceptibilities, and views susceptibility as a random variable with specified probability distribution. The models include log-probit, probit, log-logit, logit, Weibull, Mantel-Bryan and Gamma – Multihit [6, 8, 9, 10, 19]. The probit, log-probit, log-logit and logit models display a sigmoid curve in the experimental range. The Weibull model has been used extensively to predict time to failure of electrical and mechanical components, and it is more widely applied to dose-response relationship. It is capable of representing threshold and concave curves and is sensitive to the shape of the dose-response curve. It has the advantage of being able to incorporate a time-to-tumor function [6]. For more reviews on tolerance distribution models, see [6, 10-14].

4.0 Parameter Estimation Of The Weibull Model

The shape $,\alpha,$ and scale $,\beta,$ parameters of the Weibull model can be estimated using the two-parameter Weibull distribution. We shall make use of the maximum likelihood estimation (MLE) method to obtain the estimate of the shape parameter while the linear rank regression method would be used to obtain the scale parameter estimate of the Weibull model.

The probability distribution function (pdf) for two-parameter Weibull distribution is given as;

$$P(x) = \frac{\alpha}{\beta}\left(\frac{x}{\beta}\right)^{\alpha-1} \exp -\left(\frac{x}{\beta}\right)^{\alpha} \quad (1)$$

where $x = \log_e(dose).$

Application of MLE method on (1) yields

$$\hat{\beta} = \left[\frac{1}{n}\sum_{i=1}^{n} x_i^{\hat{\alpha}}\right]^{\frac{1}{\hat{\alpha}}} \quad (2)$$

and

$$\hat{\alpha} = \frac{\log\left[\frac{1}{n}\sum_{i=1}^{n} x_i^{\hat{\alpha}}\right] - 1}{\left[\frac{1}{n}\sum_{i=1}^{n} x_i - \sum_{i=1}^{n}\log_e x_i + n\log\left[\frac{1}{n}\sum_{i=1}^{n} x_i^{\hat{\alpha}}\right]^{\frac{1}{\hat{\alpha}}}\right]} \quad (3)$$

It is obvious that the shape parameter estimate in (3) will be difficult to compute for, since the above expression is an implicit function of $\hat{\alpha}$. Hence, we employ the linear rank regression method to obtain the estimate of α from the cumulative distribution function (cdf) of the two-parameter Weibull distribution.

The cdf of the two-parameter Weibull distribution is given as;

$$F(x) = 1 - \exp\left[-(x\beta^{-1})^{\alpha}\right], \ d \geq 0 \quad (4)$$

where $x = \log_e(dose)$

Some mathematical manipulations on (4) yields

$$\hat{\alpha} = \hat{b} = \frac{\sum_{i=1}^{n}(\log_e x_i)(\log_e\{-\log_e[1-F(x_i)]\}) - \frac{1}{n}\left[\sum_{i=1}^{n}(\log_e x_i)\sum_{i=1}^{n}(\log_e\{-\log_e[1-F(x_i)]\}\right]}{\sum_{i=1}^{n}(\log_e x_i)^2 - \frac{1}{n}\left(\sum_{i=1}^{n}\log_e x_i\right)^2} \quad (5)$$

where $F(x_i)$ is estimated as $\frac{rank(x_i)}{n+1}$ [15]. Equations (2) and (5) give the estimates of the scale and shape parameters of the Weibull model to be used. Hence, the estimates for LD_{50} for the Weibull model is given as

$$\hat{MLD} = \exp(\hat{x}_{50}) \quad (6)$$

where $\hat{x}_{50} = \hat{\beta}(\log_e 2)^{1/\hat{\alpha}}$ (7)

5.0 Evaluation Of Acute Toxicity Of Indomethacin In Rats Using The Weibull Model

Table 2 shows the number of deaths occurring at each dosage level of indomethacin administered to five groups of Wistrar rats for a seven-day observation.

Table 2: Lethal effects of indomethacin on Wistar rats for a seven-day observation

Dose (mg/kg)	Number at risk (n)	Number of Deaths (r)
6	10	0
12	10	4
18	10	7
24	10	9
30	10	10

Source: [2]**.**

Using the information in Table 1 to obtain the various terms in (5), we have the estimate of the shape parameter as

$\hat{\alpha} = 3.4079.$

Substituting this value into (2), we obtain the estimate of the scale parameter as

$$\hat{\beta} = \left[\frac{1}{5}\sum_{i=1}^{5} x_i^{3.4079}\right]^{\frac{1}{3.4079}} = 2.8761.$$

Further substitution of the values of $\hat{\alpha}$ *and* $\hat{\beta}$ into (7) and (6) give the estimate of MLD_{50} as

$\hat{MLD}_{50} = 13.23 mg/kg.$

6.0 Discussion

The MLD for indomethcin for rats is found to be 12mg/kg in rats with mortality for 7 days [2, 16, 18]. From above, the MLD for indomethacin which is obtained as 13.23mg/kg falls into category 2 indicating that is extremely toxic when not properly administered. Also, MLD of indomethacin obtained through the Weibull model lies in the range value (12.58 ± 1.15mg/kg) of earlier study carried out by Omogbai et al [2]. This interpretation of the MLD result of 13.23mg/kg is given by the American Society for testing and Materials [17] that any chemical substance with MLD value less than 20mg/kg but greater than 10g/kg could be considered to be extremely toxic.

7.0 Conclusion

Indomethacin as a pain-killer is a fatal and toxic substance which should not be taken as self-medication by any individual. Prescription should be done by a medical professional. It can cause impairment in the system of the individual, or death under self-medication.

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