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A New Mathematical Model for GABA-aminotransferase in human platelets by Vigabatrin

S.Lakshmi * and P.Gomathi Sundari **

* Head and Associate Professor of Mathematics, K.N.Govt.Arts College for Women,Thanjavur -613007, TamilNadu, India.

** Assistant Professor of Mathematics, Rajah Serfoji Government College, Thanjavur-613005, TamilNadu, India.

Abstract

To analyzing for some well-known generations of Weibull-related lifetime models for quick information. A brief discussion on the properties of this general class is also given. For example, the effect of the new antiepileptic drug, Vigabatrin (γ-vinyl GABA), on the platelet enzyme, GABA-aminotransferase (GABA-T) was investigated in volunteers and patients. The prolonged effect of Vigabatrin on the platelet enzyme activity would fit in with the fact that restoration of enzyme activity is dependent on regeneration of new enzyme. If the enzyme activity of platelets can be shown to reflect brain GABA-T activity, assay of the easily obtainable platelet enzyme may provide a convenient approach to assessing the pharmacological response in epileptic patients during treatment with GABA-T inhibitor drugs such as Vigabatrin. The generations of Weibull distribution is utilized for fitting the corresponding medical data, and the feedback is compared with the medical report . The curves for Reliability rate function by using Exponentiated weibull and four parameters Generalized Weibull Distribution in all the 3 cases after 5 hours reaches the zero value in the time axis and which are perfectly fitted with the medical curve. These results give good suggestions to the medical professionals.

Keywords: Failure rate function, Weibull distribution, Vigabatrin ,GABA, GABA-T.
AMS Classification: 60 G_{xx}, 62 H_{xx}, 62P_{xx}

1. NOTATION

T	Lifetime random variable
f(t)	Probability density function (pdf) of T
F(t)	Cumulative distribution function (cdf)
h(t)	hazard rate function
H(t)	Cumulative failure rate function

$$\left[H(t) = \int_0^t h(x)dx \right]$$

R(t) Reliability function [= 1-F(t)]

2.Mathematical Models

The reliability modeling, some well-known interrelationships between the various quantities such as pdf, cdf, failure rate function, cumulative failure rate function, and reliability function, for a continuous lifetime T, can be summarized as

$$h(t) = \frac{f(t)}{1-F(t)} = \frac{f(t)}{R(t)} \quad \ldots\ldots(1)$$

$$H(t) = \int_0^t h(x)dx \quad \ldots\ldots(2)$$

$$R(t) = e^{-H(t)} \quad \ldots\ldots(3)$$

Note that all the cumulative failure rate functions must satisfy the following conditions:

i. H(t) is nondecreasing for all $t \geq 0$
ii. H(t) = 0
iii. $\lim_{t\to\infty} H(t) = \infty$

Thus, knowing one of the three quantities, one can easily obtain the other two. Here we shall see how (3) facilitates the construct of Weibull-type lifetime distributions. The bathtub-shaped failure rate function plays an important role in reliability applications, such as human life, and electronic devices.

Many generalized Weibull models have been proposed in reliability literature through the fundamental relationship between the reliability function R(t) , and its corresponding cumulative failure rate function H(t). In this paper, we summarize some commonly known models, and also discuss their general properties with a hope to provide practitioners a quick overview of the most recent developments in reliability concerning the Weibull distribution. Most generalizations of the Weibull distribution stemmed from a desire to provide a better fitting of certain data sets than the traditional two- or three- parameter Weibull. One would expect many more such generalizations, modifications, or extensions to appear in years to come. Given a data set, a researcher has an onerous task to select an 'optimal' model among many possible Weibull related models.

In general, there are three steps involving the empirical modeling of data, including Weibull,

such as model selection, estimation of model parameters, and model validation. On parameter estimation, the number of parameters could be pivotal; and how easily the estimates of these parameters can be found is also an important factor. An overcomplicated Weibull model often diminishes the possibility of interpreting the parameters. Generally speaking, a Weibull model that has more than three parameters is undesirable, with the exception of mixtures of two modified Weibull distributions[1]. Thus mathematical operations on the failure rate can be obtained relatively easily, and therefore, numerical estimates of parameters become less prohibitive.

The Weibull, and related models have been used in many applications, and for solving a variety of problems from many disciplines. Although the Weibull distribution is primarily used for modeling product failures in reliability engineering, it is also sometime used to model the human aging process[2] .[3,4] have modeled human mortality using mixtures of two different modifiedWeibull distributions.We have various mixtures of two modified Weibull distributions could have a wide range of possible applications.

Case (i):

Reliability functions for Exponentiated weibull is

$$R(t) = 1 - \left[1 - exp\left(-\left(\frac{t}{\beta}\right)^{\propto}\right)^{\theta}\right],$$

$\alpha, \beta > 0, t \geq 0, \theta \geq 0$

Case (ii):

Generalized Weibull Distributions for Mudholkar, Srivastava & Kollia (1996) is

$$R(t) = 1 - \left[1 - \left(1 - \lambda\left(\frac{t}{\beta}\right)^{\propto}\right)^{1/\lambda}\right],$$

$\alpha, \beta > 0, t \geq 0$

Case (iii):

Generalized Weibull Distributions for Marshall Olkin (1997) is

$$R(t) = \frac{vexp\,[-(t/\beta)^{\alpha}]}{1-(1-v)exp\,[-(t/\beta)^{\alpha}]},\ \alpha, \beta, v > 0; t \geq 0$$

Case (iv):

Generalized inverse Weibull Distributions for Jiang et al.(2001) is

$$R(t) = 1 - exp\left[-\left(\frac{t}{\beta}\right)^{\alpha}\right],\qquad \alpha, \beta > 0; t \geq 0$$

Case (v):

Generalized Weibull Distributions for Nikulin & Haghighi (2006) is

$$R(t) = exp\left[1 - \left(1 + \lambda\left(\frac{t}{\beta}\right)^{\propto}\right)^{\theta}\right],\ \alpha, \beta > 0, t \geq 0, \theta \geq 0$$

3. Applications

Vigabatrin (γ-vinyl GABA) is a new antiepileptic drug, recently demonstrated to have a consistent anticonvulsant effect in double-blind placebo-controlled trials of patients with chronic drug-resistant epilepsy[5]. The postulated mechanism of action of Vigabatrin in epilepsy is believed to be irreversible or 'suicide' inhibition of the cerebral enzyme, GABA-aminotransferase(GABA-T), resulting in elevated brain concentrations of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) [6]. However, there does not appear to be a simple relationship between elevation of whole brain GABA concentration and seizure protection in animals and it has been suggested that elevation of the seizure threshold correlates more closely with increases in nerve terminal rather than whole brain GABA concentrations. The measurement of plasma concentrations of Vigabatrin itself are unlikely to be helpful in the management of epileptic patients who are being treated with this drug, because the intensity of drug action will be influenced not only by the dose schedule and the pharmacokinetic parameters of Vigabatrin, but also by the half-life of the target enzyme. Ideally one would like to be able to correlate the dose of Vigabatrin administered to patients with the pharmacodynamic effect of the drug on the neuro chemical changes in the brain (extent of inactivation of GABA-T, and the degree of elevation of brain GABA levels) and the clinical response (seizure control).

If the enzyme activity of platelets can be assumed to reflect brain GABA-T activity, assays of the easily obtainable platelet enzyme may provide a convenient approach to the measurement of the pharmacological response to GABA-T inhibitors in the treatment of patients with epilepsy.

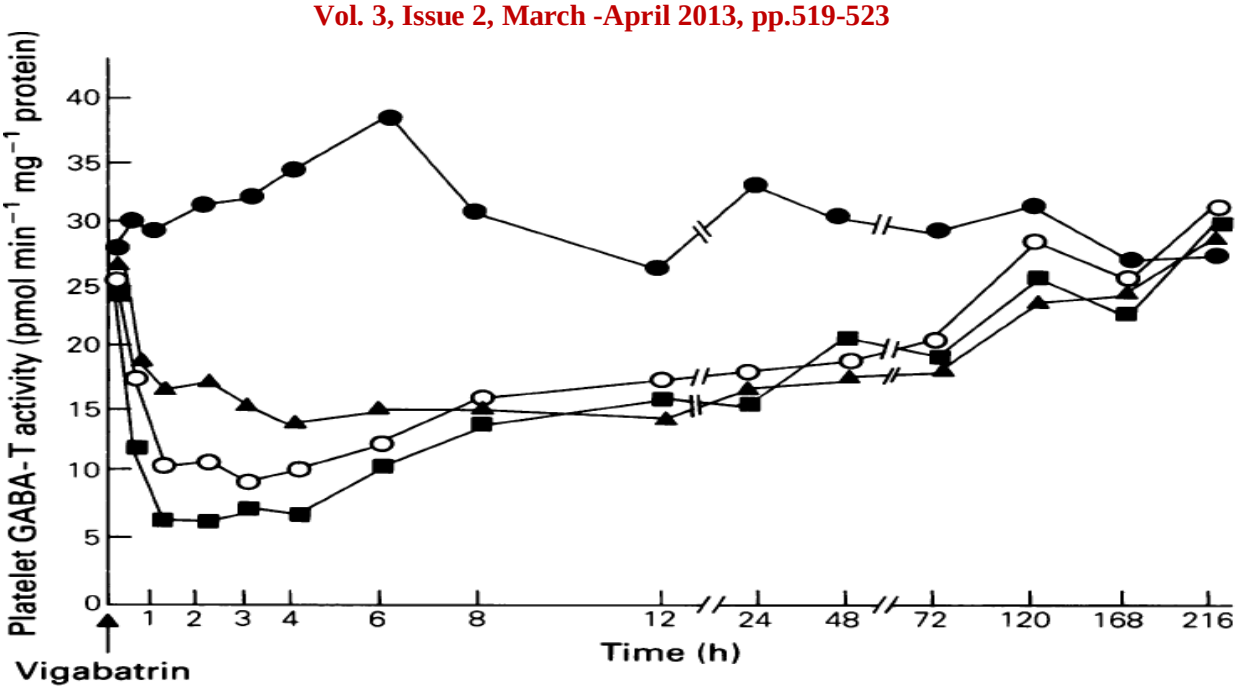


Figure 1: Mean platelet GABA-aminotransferase activity in six subjects after single doses of Vigabatrin (▲1 g, ○ 2 g, ■ 4 g) compared with control values (●). The platelet GABA-aminotransferase values following administration of Vigabatrin were significantly different from controls with all three doses at 0.5, 1, 2, 3, 4, 6 ($P < 0.01$) and 8 h ($P < 0.05$). There were significant differences between the three doses at 1,2 and 3 h ($P < 0.05$) and the mean values obtained with the three doses lay in the expected order consistent with a dose-response relationship.

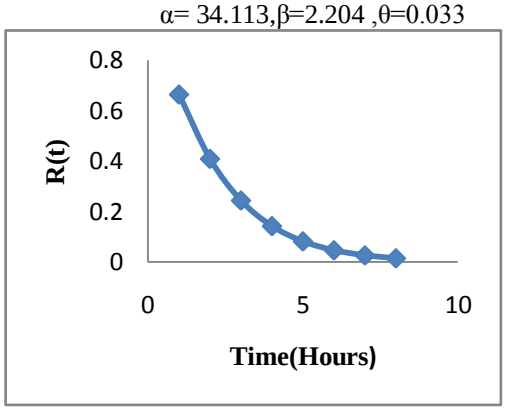
Figure 1 shows the mean levels of platelet GABA-T activity after the three different doses of Vigabatrin compared with the values obtained during the control period. This prolonged effect on the platelet enzyme would fit in with the fact that restoration of normal enzyme activity is dependent on regeneration of new enzyme. Indeed, in the patient study a week after stopping Vigabatrin the platelet enzyme activity was not significantly different from the control value.

4. Mathematical Results

Case (i)

control case

α= 34.113,β=2.204 ,θ=0.033

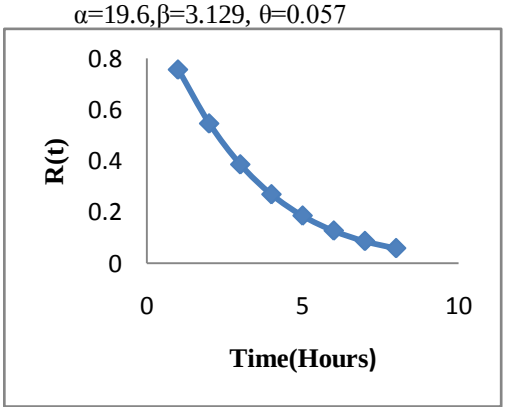


Experimental case

α=16.759 , β=2.214, θ=0.068

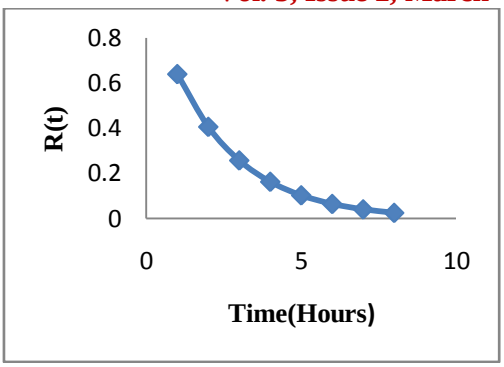
Experimental case

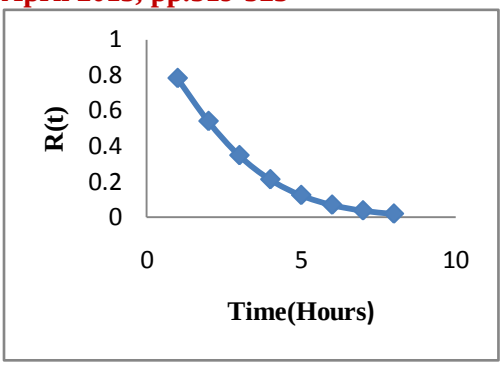
α=19.6,β=3.129, θ=0.057



Experimental case

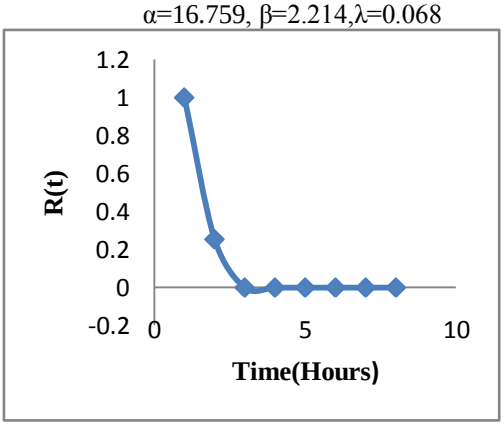
α=22.197 , β=2.89, θ=0.06





Case (iii):

control case
α=16.759, β=2.214,λ=0.068



Experimental case
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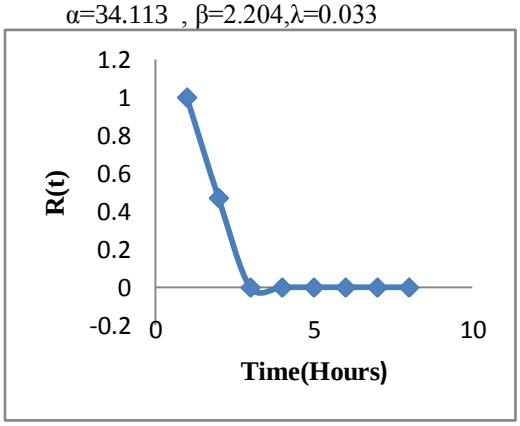
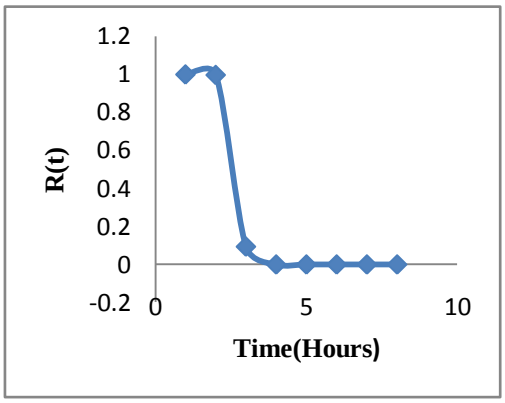
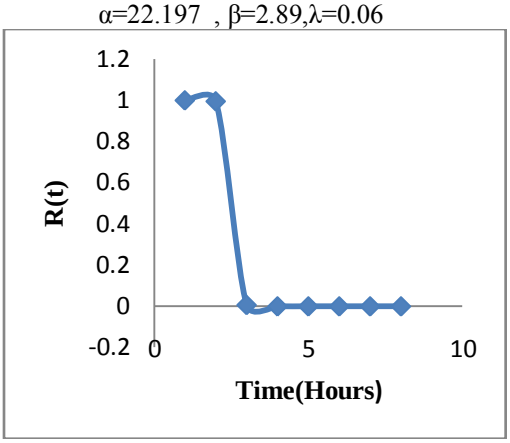


Experimental case
α=34.113 , β=2.204,λ=0.033

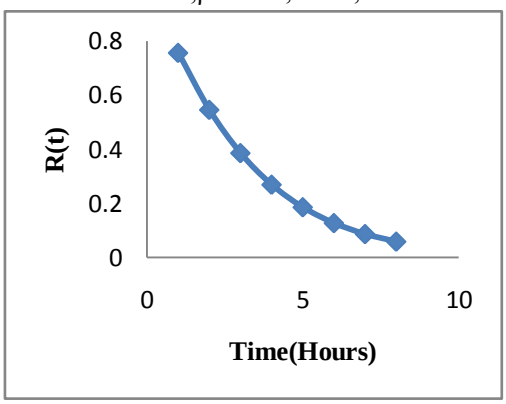


Experimental case
α=22.197 , β=2.89,λ=0.06

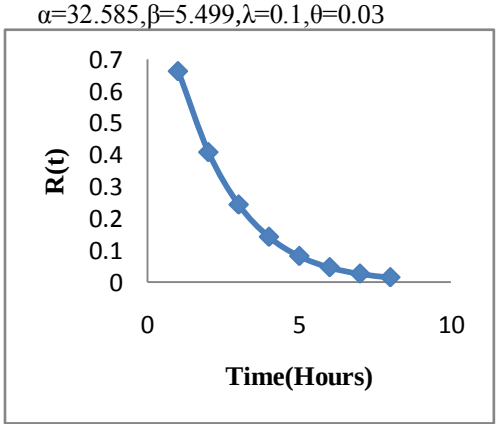


Case (v) :

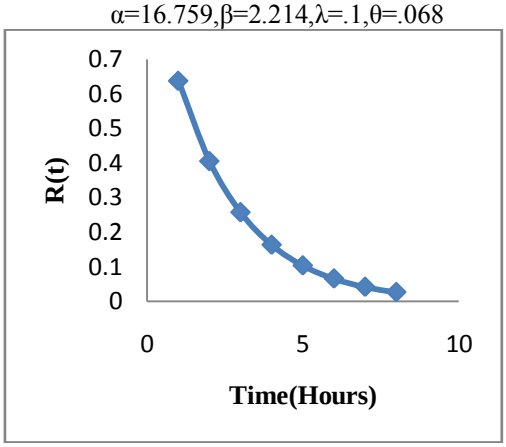
control case
α=19.6,β=3.129,λ=0.1,θ=0.057



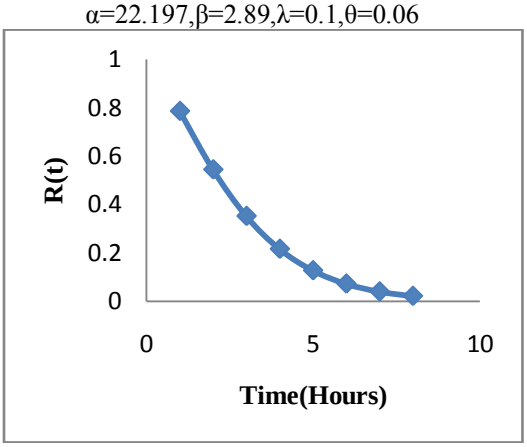
Experimental case
α=32.585,β=5.499,λ=0.1,θ=0.03



Experimental case
α=16.759,β=2.214,λ=.1,θ=.068



Experimental case
α=22.197,β=2.89,λ=0.1,θ=0.06



In the case of Exponentiated weibull the Reliability rate decreases from 1 to 0. After the time of 5 hours and the Reliability reaching the saturation point zero. In the Generalized Weibull Distributions for Marshall Olkin the Reliability rate decreases suddenly and reaches the value zero nearing to 5 hours . In the Four parameter Weibull Distributions for Nikulin & Haghighi shows that the Reliability rate after the time point of 5 hours reaches the zero level in the time axis .Similarly we can find figures for the cases of Generalized Weibull Distributions for Mudholkar,Srivastava&Kollia and Generalized inverse Weibull Distributions for Jiang.

5. Conclusion

Mean platelet GABA-aminotransferase activity in six subjects after single doses of Vigabatrin (▲1 g, ○ 2 g, ■ 4 g) compared with control values (●). The platelet GABA-aminotransferase values following administration of Vigabatrin were significantly different from controls with all three doses at 0.5, 1, 2, 3, 4, 6 ,($P < 0.01$) and 8 h ($P < 0.05$). There were significant differences between the three doses at 1,2 and 3 h ($P < 0.05$) and the mean values obtained with the three doses lay in the expected order consistent with a dose-response relationship. These values are compared in the 5 cases of mathematical distribution and corresponding results have been obtained. The curves for Reliability rate function by using Exponentiated weibull and four parameters Generalized Weibull Distribution in all the 3 cases after 5 hours reaches the zero value in the time axis and which are perfectly fitted with the medical curve. These results give good suggestions to the medical professionals.

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