International Journal of Sciences & Applied Research

www.ijsar.in

A mathematical model for finding the effect of Lignocaine on Frusemide in Arginine Vasopressin level by using BGTLNB model

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Abstract

In this paper to analyzing for some BGTLNB Model if a random vector (Y, N) with the stochastic representation $(Y,N)\overset{d}{=}\left(\bigvee_{i=1}^{N} E_i \vee R, N\right)$ is discussed, where N is a negative binomial, and the $\{E_i\}$ are IID exponential variable $f(x) = \beta e^{-\beta x}$, $x > 0$ is a generalized exponential variable with CDF $P\left(R_t \le x\right)=\left(1-e^{-\beta x}\right)^t$ and all the variables are mutually independent. This distribution is known as bivariate distribution with generalized truncated logistic and negative binomial (*BGTLNB*) distribution with parameters $t > 0$, $\beta > 0$ and $p \in (0,1)$. This model is used for our application part. Here effect of the infusion of lignocaine on frusemide induced Arginine vasopressin, the infusion of lignocaine generated mean steady state serum concentration levels, compared to the influence of frusemide alone on average Arginine vasopressin plasma levels are taken as random variables and fitted with the above distribution and obtained from the corresponding mathematical result.

Keywords: Arginine vasopressin, NB variable, *BGTLNB*, Lignocaine, Frusemide

Mathematical model

A random vector (Y, N) with the stochastic representation

$$(Y,N)\overset{d}{=}\left(\bigvee_{i=1}^{N} E_i \vee R, N\right) \quad \text{------ (1)}$$

where, the $\{E_i\}$ are IID exponential variables $f(x) = \beta e^{-\beta x}$, $x > 0$, R is a generalized exponential variable with the CDF $P\left(R_t \le x\right)=\left(1-e^{-\beta x}\right)^t$, and N is a NB variable. $P\left(N=k\right)=\frac{\Gamma(k+t)}{k!\Gamma(t)}p^t(1-p)^k$, $k = 0, 1, 2, \ldots\ldots$ with all the variables mutually independent, is said to have a BGTLNB distribution with parameters $t > 0$, $\beta > 0$ and $p \in (0,1)$. This distribution is denoted by BGTLNB (t, β, p).

The joint pdf of (Y, N) ~ BGTLNB (t,β,p) can be derived through a conditioning argument. Given N = n, Y is the maximum of n IID EXP (β) variables and a generalized exponential variable with CDF P $(R_t \le x) = (1 - e^{-\beta x})^t$ so that the CDF [14] and the PDF of Y are

$$F_{Y/N}(y/n) = (1 - e^{-\beta y})^{n+t}, \quad y > 0, \qquad \text{------} \quad (2)$$

and

$$f_{Y/N}(y/n) = (n + t)\beta e^{-\beta y}(1-e^{-\beta y})^{n+t-1}, \quad y > 0 \qquad \text{------} \quad (3)$$

respectively. Since N is a NB variable with the pdf P $(N = k) = \frac{\Gamma(k+t)}{k!\Gamma(t)} p^t (1-p)^k$,k = 0, 1, 2,….the joint PDF of this model is of the form

$$f(y, n) = \frac{\beta(n+t)\Gamma(n+t)}{n!\Gamma(t)} e^{-\beta y}(1-e^{-\beta y})^{t+n-1} p^t (1-p)^n$$

, y > 0, n = 0, 1, 2…. ------ (4)

Note that when t = 1 this reduces to the pdf of the BTLG (β, p) distribution shifted by (0, -1). Similar conditioning leads to the CDF of Y:

P $(Y \le y) = \sum_{n=0}^{\infty} \mathrm{P}\left(\bigvee_{j=1}^{n} E_j \vee R \le y \right) \mathrm{P}(\mathrm{N} = \mathrm{n}) = (F(y))^t G_N(F(y))$

where F(.) is the CDF of the $\{E_i\}$ and G_N (.) is the generating function of N. After further simplifications we obtain

$$F_Y(y) = \left(\frac{p(1-e^{-\beta y})}{p + (1-p)e^{-\beta y}} \right)^t = \left(\frac{p}{q} \frac{1-q}{1-p} \right)^t$$

, y ≥ 0 ------ (5)

with q defined in q = q(p,β,y) = p + (1-p) $e^{-\beta y}$ ∈ (0,1). Since this is a power of the truncated logistic CDF $F_Y(y) = \left(\frac{p(1-e^{-\beta y})}{p + (1-p)e^{-\beta y}} \right)^t = \left(\frac{p}{q} \frac{1-q}{1-p} \right)^t$, y ≥ 0 in analogy to the generalized exponential distribution [5], we shall refer to this as a generalized truncated logistic distribution (GTL) with shape parameter t > 0 and scale parameter β > 0.

To obtain the joint CDF of the BGTLNB model, we start by writing

P $(Y \le y, \mathrm{N} \le \mathrm{n}) = \sum_{k=0}^{n} \frac{\Gamma(k+t)}{k!\Gamma(t)} p^t (1-p)^k \int_0^y \beta(k-t) e^{-\beta x}(1-e^{-\beta x})^{t+k-1} dx$

for any y > 0 and n = 0,1,2,…….. Since the integral above simplifies to $(1-e^{-\beta y})^{k+t,}$ after further implications we obtain

P $(Y \le y, \mathrm{N} \le \mathrm{n}) = \left(\frac{p}{q} \frac{1-q}{1-p} \right)^t \sum_{k=0}^{n} \frac{\Gamma(k+t)}{k!\Gamma(t)} q^t (1-q)^k$

y > 0, n = 0,1,2…… ---- (6)

with q given by q = q(p,β,y) = p + (1 − p) $e^{-\beta y}$ ∈ (0,1) as before. Note that the summation above is the same as the probability P ($N_q \le n$), where N_q is a NB variable with parameter t > 0 and q ∈(0, 1).

Application

If more than three decades, lignocaine, a local anaesthetic, has been used in therapeutics as an antiarrhythmic agent [13]. Although, the electrophysiological properties of lignocaine are well known and acknowledged in the treatment of acute ventricular arrhythmias [10] other effects of

lignocaine, such as its influence on haemodynamics and on hepatic vascular resistance, are poorly characterized. Concerning the effect of lignocaine on peripheral haemodynamics, in healthy subjects, low levels (< 3.4μg ml^{-1}) of lignocaine produced a concentration-dependent elevation in peripheral blood flow resulting from a decrease in peripheral vascular resistance.

On the other hand, venous capacitance rose until lignocaine concentrations were around2μgml^{-1}, but decreased at higher concentrations when systolic blood pressure increased [11]. The net effect of lignocaine on haemodynamics appears modulated by individual baseline status, since in patients with cardiac failure, an intravenous dose of 50 or 100 mg of lignocaine induced a small decrease in the cardiac index, stroke volume and work indices, as well as in arterial blood pressure.With respect to the effect of lignocaine on hepatic blood flow, in healthy volunteers, lignocaine appears to produce a concentration-dependent rise in hepatic blood flow, secondary to a fall in splanchnic vascular resistance and an increase in cardiac output [12]. In anaesthetized dogs, the infusion of lignocaine for 24 h increases hepatic blood flow [9].

These results contrast with those observed in other animals or in patients with heart failure, where lignocaine does not affect, hepatic, blood flow [2, 4]. Theoretically, in healthy volunteers, the lignocaine-induced decrease in splanchnic vascular resistance could be caused by: (a) a direct effect on smooth muscle vasculature (b) an effect on the central nervous system [1] or (c) an effect on factors regulating the tonus of the splanchnic vascular bed [11].Since in healthy volunteers, the effect of lignocaine is much more marked on hepatic blood flow than on peripheral resistance or cardiac output [12]. We hypothesized that lignocaine affects the release or effect of factors like arginine-vasopressin (AVP), the activity of which predominantly occurs on the spanchnic vascular bed. The present study was designed to document in conscious healthy animals whether lignocaine alters (a) baseline plasma AVP levels, and (b) the secretion of AVP induced by a potent stimulus.

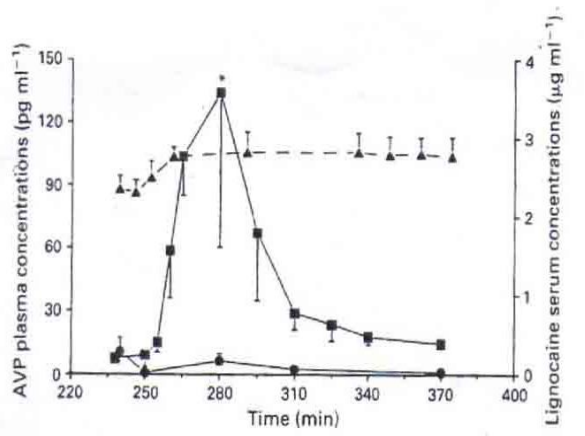

Figure 2 Effect of an infusion of lignocaine (130 μg min^{-1} kg^{-1}) on frusemide-induced arginine-vasopressin (AVP) levels ($n = 7$) (●), compared to the influence of frusemide alone ($n = 7$) (5 mg kg^{-1}) on average AVP plasma levels (■). The infusion of lignocaine generated mean steady state serum concentrations of 2.83 μg ml^{-1} (▲). Frusemide was injected 250 min after the beginning of the infusion of sodium chloride/glucose (frusemide alone experiment) or of the infusion of lignocaine. Serum AVP and lignocaine levels were estimated 238 min after the beginning of the infusions. Vertical bars are s.e. $*P < 0.05$ compared to baseline values.

Frusemide was used to induce AVP secretion, because the depletion of volume produced by frusemide produces a rapid and potent increase in AVP plasma concentrations [3]. Furthermore, the choice of frusemide was reinforced by the fact that in clinical practice, lignocaine and frusemide are frequently used simultaneously. In the current study, lignocaine diminished baseline AVP plasma levels almost sevenfold. This fall in AVP cannot be attributed to changes in plasma osmolality, since the latter remained stable, or to the infusion of sodium chloride-glucose. In the rabbit, exogenous AVP has a very high systemic clearance, about 45ml $min^{-1}kg^{-1}$ and both the splanchnic bed and the liver appear to account for at least half of it. Therefore, the clearance of AVP should theoretically be considered as a blood-flow-dependent event.

Accordingly, increases in splanchnic blood flow should enhance the clearance of AVP. Since lignocaine did not increase hepatic blood flow, we believe that the lignocaine-induced decrease in AVP plasma concentrations is not associated with an increase in AVP clearance. Therefore, we must assume that lignocaine decreases the rate of secretion of AVP levels by changing liver blood flow is reasonable if we bear in mind that frusemide reduced liver blood flow significantly and following the administration of lignocaine, AVP plasma levels were reduced, instead of increased. Lignocaine prevented the increase in AVP plasma concentrations induced by frusemide, probably because of a reduction in AVP secretion by the hypothalamo-neurohypophysial axis rather than an increase in AVP clearance. A 5 mg kg^{-1} dosage of frusemide resulted in a volume depletion of 58 ± 7ml in 1 h, equivalent to the diuresis produced. As mentioned above, this volume depletion will stimulate several systems, all capable of enhancing the release of AVP. The fact that lignocaine was able to inhibit the stimuli responsible for the frusemide-induced secretion of AVP, supports the hypothesis that lignocaine inhibits AVP secretion directly at the hypothalamo-neurohypophysial axis.

Mathematical result

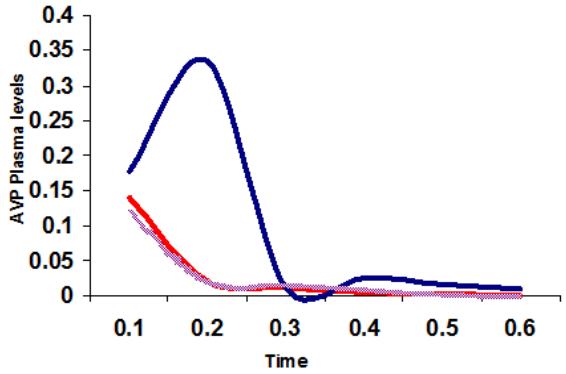

Fig: 3.1

Conclusion

As a result the curves for fig 3.1 here we conclude that the infusion of lignocaine generated mean steady state serum concentration increases for certain levels and reached the maximum levels at the time point (280 minutes) and then decreases suddenly at the time axis in consecutive times. The other two variables simultaneously decrease to the time axis from the certain highest time is used for our application part by *BGTLNB* distribution model. Here effect of the infusion of lignocaine on frusemide induced Arginine vasopressin, the infusion of lignocaine generated mean steady state serum concentration levels, compared to the influence of frusemide alone on average Arginine vasopressin plasma levels are taken as random variables.

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