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MATHEMATICAL MODEL FOR RENIN INHIBITOR IN NORMAL HUMANS

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Abstract:

Interpretation of renin-angiotensin blockade with angiotensin converting enzyme inhibitors is potentially confounded by their multiple effects. We used a selective renin inhibitor to explore the renal and endocrine effects of angiotensin II in healthy men. Each received 90-minute enalkiren infusions at 2-day intervals, on a low (10 mmol, 16 subjects) and high (200 mmol, 12 subjects) salt diet. Plasma renin activity, immunoreactive plasma angiotensin II and aldosterone concentratitons, inulin, and *p*-aminohippurate clearance were measured by standard methods. Plasma renin activity fell at 0.1 μg/kg, but the threshold for biologic effect was 256 μg/kg, where plasma immunoreactive angiotensin II and aldosterone concentration fell, and renal plasma flow rose ($p< 0.01$). We confirm that conventional plasma renin activity measurement is misleading in humans receiving a renin inhibitor.Bivariate distribution is applied in PRA and to find unique positive solution for plasma of renin.

Key Words: PRA, Enalkiren, Product of Weibull Distribution & Multivariate Distribution.

1. Introduction:

Pharmacological interruption of the renin-angiotensin system has played a special role in attempts to define its role in normal physiology and in the pathogenesis of disease. The reason is fundamental. Ablation of the source of a hormone followed by replacement has been crucial to defining the hormone's contribution [5]. In the case of the renin-angiotensin system, where the kidney is not only the source of the hormone but also a determinant of sodium homeostasis, the value of the ablation experiment has been limited. Pharmacological interruption of this sytem, therefore, has essentially replaced ablation as a pivotal step. The most widely used agents, the angiotensin converting enzyme (ACE) inhibitors, block an enzyme that has multiple functions, including degradation of kinins and consequent prostaglandin formation [4,10]. Thus, the specificity of responses to ACE inhibition is suspect. The angiotensin antagonists available until recently were partial agonists with substantial angiotensinlike activity, which limited their usefulness [6]. Although a new family of angiotensin antagonists has been developed [9], little is known about their action in humans.

2. Material and Discussion:

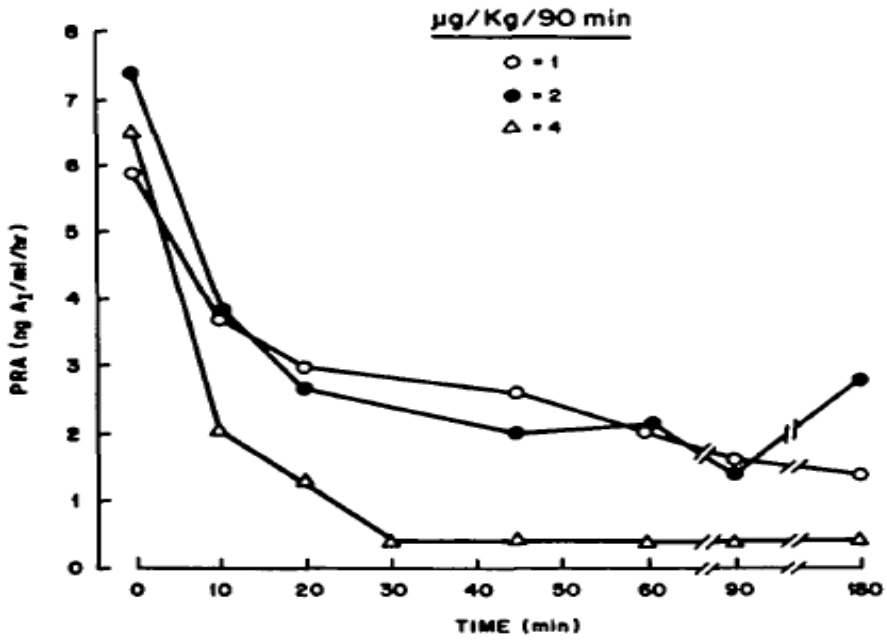

Figure 1: Line graph showing change in plasma renin activity (PRA) during enalkiren infusion in subject who received the lowest doses administered (1, 2 and 4 μg/kg/90 min)

The subjects were 16 healthy men ranging in age from 22 to 48 years (35 ± 2 years). All were free of cardiovascular, renal and endocrine disease and were within 20% of ideal body weight, with an average weight (± SEM) of 70.6 ± 2.3 kg. After an outpatient evaluation, all were studied during a 14 day.

All subjects were placed on constant isocaloric diets throughout the entire hospitalization, including a 10 meq daily sodium intake for the first 11 days. In 12 of the subjects, dietary sodium intake was then increased to 200 meq/day for 2-3 days before the last protocol day. Daily dietary potassium (100 meq) and fluid (2,500 ml) intake were constant on both diets. Twenty-four-hour urine samples were collected daily and were analyzed for sodium, potassium, and creatinine. When 24 hour urine sodium matched intake (usually on day 5 for the 10 meq sodium diet and day 3 for the 200 meq sodium diet), responses to renin inhibitor infusions were assessed.

Restriction of salt intake led to the anticipated fall in sodium excretion and activation of the renin-angiotensin – aldosterone system. Blood pressure did not change with changes in salt intake. Administration of the renin inhibitor in the subjects in balance on a low salt diet led to dose-related falls in plasma aldosterone and irAng II concentration, and an increase in renal plasma flow.

The pattern of changes in PRA in relation to enalkiren dose differed strikingly from the response of plasma irAng II and aldosterone concentration, and renal plasma flow. The lowest dose used, 1μg/kg/90 min, resulted in a rapid fall in PRA, to about 50% in 10 minutes, but it remained in the measurable range, at 2-3 ng angiotensin I/hr throughout the remainder of the infusion. The 4 μg/kg/90 min doses dropped PRA by over two thirds in 10 minutes, and the level fell to the threshold for the method in 30 minutes (figure 1). All doses in all subjects thereafter rapidly led to immeasurable PRA levels, the time to nadir decreasing with increasing dose.

3. Application:

Renin inhibition induced an anticipated pattern of response, including a dose –related fall in plasma irAng II concentration. The increase in renal plasma flow and fall in plasma aldosterone concentration occurred over the same dose range effective in reducing Ang II formation, although the threshold for an increase in renal plasma flow was somewhat lower. Also as anticipated, the changes were substantially more striking when the subjects were studied on a low salt diet, which activated the renin-angiotensin-aldosterone system. The blood pressure fall was limited, but ACE inhibitors also induced a minimal blood pressure fall in normotensive recumbent subjects on an identical diet. Discrepancies between the biological response to a renin inhibitor.

4. Mathematical Model – I:

In [8] Estimation of the Weibull distribution parameters and its applications were well demonstrated earlier [1, 7]. The product of the Weibull density functions and a random variable constructed based on such products are studied. Let X_i be the Weibull random variable with parameter α_i, β_i for all $i = 1,2,3,\ldots,n$ and

$$f(X_i) = (\beta_i / \alpha_i)(X_i / \alpha_i)^{\beta_i - 1} \exp\{-(X_i / \alpha_i)^{\beta_i}\},$$

Where $\alpha_i, \beta_i > 0$.

Theorem 4.1:

For given $\mathcal{R}$ as above, $\sum_{k=1}^{i-1} -(Y_{ik} / \alpha_{ik})^{\beta_{ik}} < \sum_{k=i+1}^{n} -(Y_{ik} / \alpha_{ik})^{\beta_{ik}}$.

Proof:

Taking logarithms for

$$\exp\left\{-m^2 z\beta_{ii} / \alpha_{ii} \sum_{k=1}^{i-1} (Y_{ik} / \alpha_{ik})^{\beta_{ik}}\right\}$$

$$< P(\mathcal{R} > z) \exp\left\{m^2 z\beta_{ii} / \alpha_{ii} \sum_{k=i+1}^{n} (Y_{ik} / \alpha_{ik})^{\beta_{ik}}\right\}$$

$$< \exp\left\{m^2 z\beta_{ii} / \alpha_{ii} \sum_{k=i+1}^{n} (Y_{ik} / \alpha_{ik})^{\beta_{ik}}\right\}$$

and through some algebraic manipulations we arrive at the required inequality.

The Weibull distribution has been shown to be the best model for life testing problems. Bivariate and multivariate forms were also explored by the researcher in classical way [2]. Lee discussed properties of the bivariate distributions of the form

$$F(X_1, X_2) = \exp\{-(\alpha_1 X_1^{\beta} + \alpha_2 X_1^{\beta})^{\mu}\}$$

For $\alpha_i > 0$, $X_i \le 0$, $i = 1,2$, $\beta > 0$ and $0 < \mu \le 1$.

5. Result:

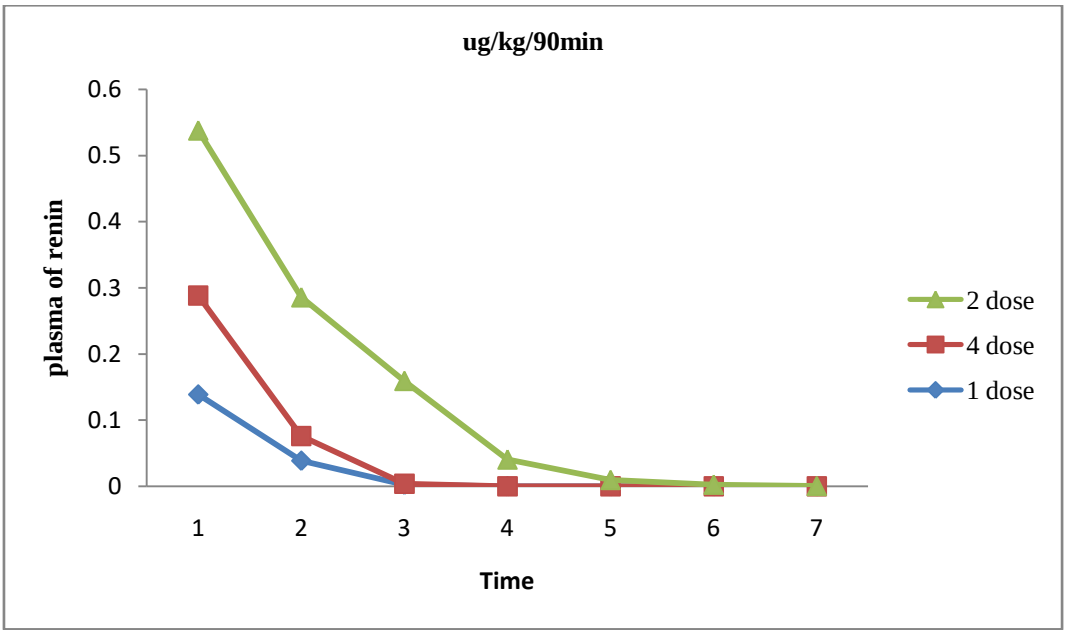

Figure 2: Bivariate distribution of plasma renin activity

6. Mathematical Model – II:

Notation and Assumptions:

C0 – Ordering Cost
Cp– Purchase Cost
Ca– Amelioration Cost
Ch– Holding Cost
g(T) – Auxillary Function
$T^{\#}$ - Unique Positive Solution

In [3] the significant number of deterioration phenomena of inventory items in practice, much research has been performed to develop vaarious deterioration models. Inventory models were proposed to deal with deteriorating items where the amount of stock decreases gradually over time.

Since a weibull distribution can be used to effectively describe the life –span of a product by varying parameter values, it has been applied to the modeling of the product life cycle for inventory management in recent years.

Substituting $I_0 = I(0) = R\int_0^T e^{-\alpha x^{\beta}} dx$ into $TC(T) = I_0\left(\frac{C_p - C_a}{T} + \frac{C_h}{2}\right) + RC_a + \frac{C_0}{T}$ and then taking the first derivative yields.

$$\frac{dTC(T)}{dT} = \frac{R}{T^2} f(T) \qquad \ldots (1)$$

With an auxiliary function $f(T)$ where,

$$f(T) = (C_p - C_a)\left[Te^{-\alpha T^{\beta}} - \int_0^T e^{-\alpha x^{\beta}} dx\right] + \frac{C_h}{2} T^2 e^{-\alpha T^{\beta}} - \frac{C_0}{R} \qquad \ldots (2)$$

Examining the properties of $\frac{dTC(T)}{dT}$ can be simplified to examining the properties of $f(T)$. The inequality $e^{-\alpha T^{\beta}} < e^{-\alpha x^{\beta}}$ holds for $0 < x < T$, and thus $\int_0^T e^{-\alpha x^{\beta}} dx > \int_0^T e^{-\alpha T^{\beta}} dx = Te^{-\alpha T^{\beta}}$. Since $C_p > C_a$ and $\lim_{T\to\infty} T^2 e^{-\alpha T^{\beta}} = 0$ with $\beta > 0$, it implies $f(\infty) < 0$.

Taking the derivative of $f(T)$ and extracting the positive multipliers, the rest of terms can be replaced with an auxiliary function $g(T)$ as follows

$$\frac{d}{dT} f(T) = \alpha\beta T^{\beta} e^{-\alpha T^{\beta}} g(T) \qquad \ldots (3)$$

Where,

$$g(T) = \frac{C_h}{\alpha\beta} T^{1-\beta} - \frac{C_h}{2} T - (C_p - C_a). \qquad \ldots (4)$$

To further examine the expression of Eq. (4), the inventory model is divided into three cases by the ranges of $\beta : 0 < \beta < 1, \beta = 1,$ and $\beta > 1.$

If $0 < \beta < 1$

For the first case with $0 < \beta < 1$, obtained from Eq. (4), it follow that,

$$\frac{d}{dT} g(T) = \frac{C_h(1-\beta)}{\alpha\beta} \left(\frac{1}{T^{\beta}} - \frac{\alpha\beta}{2(1-\beta)} \right) \qquad \ldots (5)$$

To simplify the expression, the unique positive root of the equation $dg(T)/dT = 0$ is denoted as $T^{\#}$, yielding

$$T^{\#} = \left(\frac{2(1-\beta)}{\alpha\beta} \right)^{\frac{1}{\beta}} \qquad \ldots (6)$$

From Eq. (5), it can be observed that $\frac{d}{dT} g(T) > 0$ for $0 < T < T^{\#}$ and $\frac{d}{dT} g(T) < 0$ for $T > T^{\#}$. Hence, as T increases, function $g(T)$ increases for $0 < T < T^{\#}$ and decreases for $T > T^{\#}$. Depending on the sign of $g(T^{\#}).\beta$

7. Result:

α = 2.930	β = 0.391	$T^{\#}$= 1.256
α = 3.089	β = 0.451	$T^{\#}$= 0.5898
α = 1.2029	β = 0.821	$T^{\#}$= 0.3515

8. Conclusion:

The Ang II makes a pivotal contribution to the state of the renal blood supply and to aldosterone release in normal men when the renin system is activated by restriction of salt intake. Renin inhibition is likely to be an important complement to ACE inhibition in dissecting the contribution of this system to the pathogenesis of human disease. We found bivariate distribution for Renin and also found unique positive solution of Renin due to strees.

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