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The Steady state and the Transient behavior ofthe model to predict the tolerance level when the administration of PEG-GHRH and GHRHin human

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ABSTRACT

The steady state and the transient behavior of the model to study the administration of PEG-GHRH to provide increased stability compared with the currently available GHRH.This study aimed to find the inability and to predict difference of tolerance when PEG-GHRH and GHRH were administered, The application part is fitted with the Mathematical model and the conclusion is compared with the medical report.

Key words: GH, GHRH, Steady state.
Mathematical subject classification:62 G_{xx} ; 62 H_{xx}; 62 HP_{xx}

1. INTRODUCTION

Thorner and colleagues were intrigued by observations of two patients with ectopic growth hormone – releasing hormone (GHRH) secretion, arising either from a pancreatic islet tumour or from a metastatic carcinoid tumour,that gave rise to acromegaly [17,18].Deposit persistently elevated GHRH levels throughout a 24 – h observation period, the pattern of growth hormone (GH) release remained

pulsatile.This suggests that factors other than GHRH,such as somatostatin,are likely to be involved in regulating the pulsatile pattern of GH secretion.GHRH is a 44- amino acid peptide secreted by the hypothalamus that regulate the expression, synthesis and release of GH from the somatotroph cells of the anterior pituitary.A peptide consisting of the first 29 amino acids of human GHRH retains the biological activity of the full- length peptide and has been used clinically for the treatment of GH deficiency in children. More recently, the potential of GHRH to reverse the age-related decline in the function of the somatotrophic GH—insulin-like growth factor (IGF)-I axis has been evaluated. Conjugation with polyethylene glycol (PEG;PEGylation) is a widely used approach for improving the stability of peptide and protein drugs and a number of PEGylated molecules are approved for clinical use.Therefore,we applied this technique with the objective of obtaining a more stable form which improved physico-chemical andbiological characteristics compared with the parent molecule.

In particular, PEGylation was aimed at increasing stability to degradation by the pro-tease dipeptidylpeptidase IV,potentially improving bio-availability and prolonging plasma half-life and hence increasing the pharmacodynamic response of the somatotrohic axis.

Consequently, the improved pharmacokinetic profile of PEG-GHRH was assessed by means of its impact on GH secretion. PEG-GHRH has a higher solubility in water and aqueous buffers compared with GHRH.Due to the presence of the PEG chain, the product has a pro-longed half – life in plasma [8].As a result, a single injection of PEG-GHRH generates, in animal models, a sustained pharmacodynamic response characterized by multiple GH peaks.

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1.1 REPEATED-DOSE STUDY IN ELDERLY SUBJECTS

There was a pronounced effect on GH secretion following PEG-GHRH treatment in the repeated – dose study.Figure 4 shows the median response following injection of PEG –GHRH at 2 mg and 4 mg and after placebo.Interestingly,the response on day 6 appeared more pronounced that the following the first PEG – GHRH dose.A stastistically significant effect of PEG –GHRH on AUE (Area under the effect vs time curve)was found for all time intervals over which AUE was computed.Both PEG –GHRH doses gave a significantly higher AUE compared with placebo.

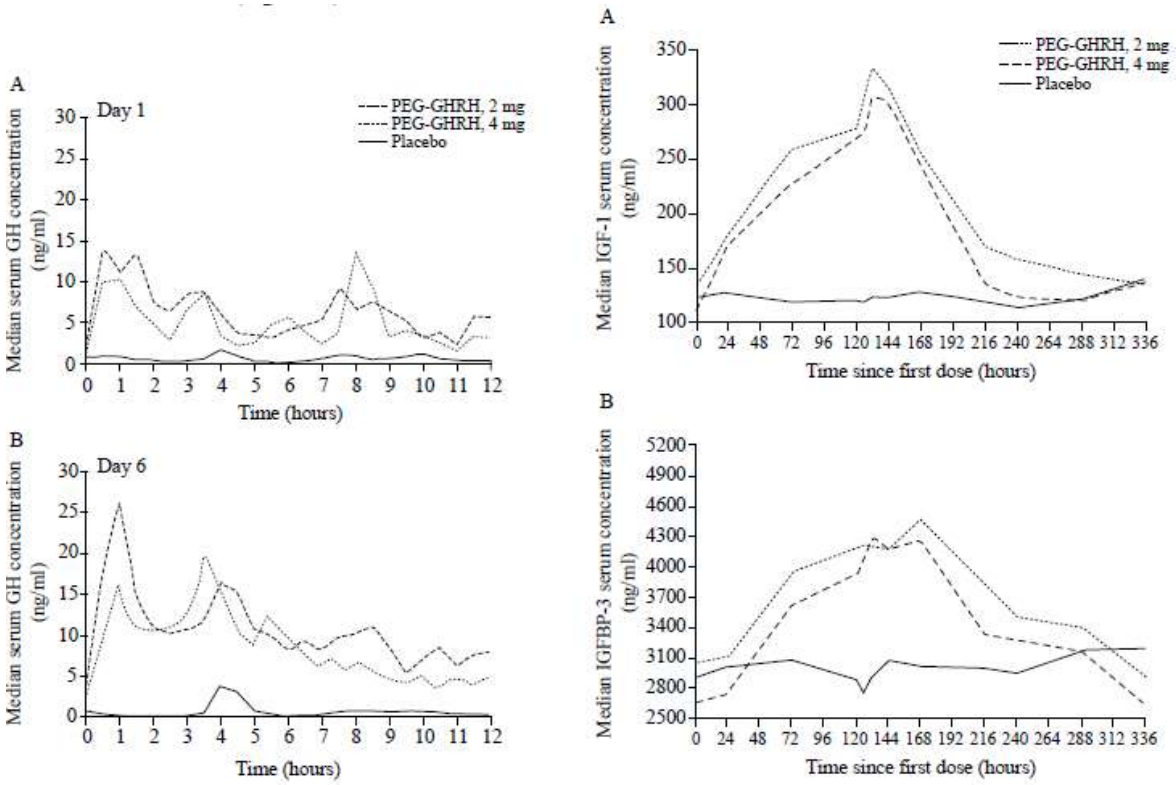

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Figure- 1 Median GH serum concentration time-course following repeated subcutaneous administration of PEG-GHRH,2mg or 4mg or placebo,during the first (A) and last (B) treatement day.

Figure -2 Median GH serum concentration time-course for (A) IGF-I and (B)IGFBP-3 following six daily injections of PEG-GHRH,2mg or 4mg or placebo.

A significant gender effect and a gender by treatment interaction were found for AUE_{0-12} and AUE_{6-12}.The GH response to PEG-GHRH was statistically higher in women than in men following the adminstration of 2 mg PEG – GHRH.A significant day effect was found for AUE_{0-12} and AUE_{6-12}, both of which were higher on day 6 than one day 1.Serum IGF-I remained constant following placebo adminstration and increased following repeated PEG-GHRH administration (Fig.1A).Values remained above pre-treatment levels for approximately 7 days after cessation of treatment.Statistical analysis taking the baseline level of IGF-I (Insuline like growth factor) as a covariate revealed a significant effect of treatment on IGF –I concentration before the sixth PEG – GHRH dose,maximum concentration reached and integrated AUE over 1 week (all $P > 0.0001$).Gender effect and gender-by treatment interaction reached significance for the two concentration parameters (women showing a stronger response than men),but not for the integrated AUE.Although serum IGF-I in all subjects responded more strongly to PEG – GHRH than to placebo, a large variability in response was observed.There was no significant correlation between an individual's GH and the IGF-I response to PEG- GHRH.Parallel to the changes in serum IGF-I levels,IGFBP-3 also increased following repeated PEG-GHRH treatment and serum concentrations remained above pre-treatment values for about 1 week after the last PEG-GHRH dose (Fig.2B).Statistical analysis revealed a significant treatment effect for concentration before the sixth PEG-GHRH dose,the maximum concentration reached and the integrated AUE for 1 week after the sixdose (AUE_{0-168} ; all $P > 0.0001$).For all markers (serum GH,IGF-I and IGFBP-3),women presented greater response to PEG-GHRH than did men for some or all measures of response.In many cases,the difference

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between females and males reached staistical significance.This difference was only partly explained by differences in body weight.

2. MATHEMATICAL MODEL

The inability to predict the secretion of PEG-GHRH and GHRH and difficulty in applying the traditional valuation methods. But the transient behavior of the model focuses on both transient and steady state behavior of the secretion of PEG-GHRH and GHRH,which in turn is modeled as a birth-death process.

2.1 NOTATION OF THE MODEL I &II

GHRH - Growth hormone-releasing hormone

PEGGHRH - Polyethylene glycol-conjugated Growth hormone-Releasing hormone

λ - Appreciation of the effects of secretion of PEG-GHRH

μ - Depreciation of the effects of PEG-GHRH

x(t) - Variation terms x(t) are different (i.eappreciation or depreciation

of GHsecretion) of a individual with reference to time.

h - Assessment period of PEG-GHRH

g - PEG-GHRH output due to some other factors.

π_n, n = 1,2,…-Steady – State measure of a birth – death process

n - Total number of appreciation and depreciation in the figure.

F(n) - The tail probability of the steady – state distribution.

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2.2 THE TRANSIENT BEHAVIOR OF THE MODEL

The speed of convergence of a birth – death process can be measured by the decay parameter.

$$\gamma = \mathrm{Sup}\left\{\alpha \geq 0; P_{i,j}(t) - \left(\frac{\Pi_j}{S}\right) = o(e^{-\alpha t}) \text{foralli}, j \geq 1\right\}:$$

Where, as before, Pij (t) is the transition probability at time t and $\frac{\Pi_j}{S}$ is the steady state probability [4].The decay parameter γ affects the convergence in an exponential way. In other words, a small difference in γ can have a remarkable effect on the speed of convergence, which in turn suggests that, the steady-state analysis of the size distribution in our model based on the birth-death process is only relevant when the decay parameter is large [9]. In addition, since the infinitesimal generator of the birth-death process is an infinite – state matrix, the analysis of the convergence rate is different from that for finite-state Markov chains[11].

2.3 RESULT (THE DECAY PARAMETER)

For the birth-death process in the model, if h = 0, then the decay parameter γ is equal to μ-λ; otherwise, if h>0 then

$$\mu-\lambda \leq \gamma < \mu-\lambda + h\left[1 - \min\left(\frac{\lambda}{\mu}, \frac{\lambda+g}{\mu+h}\right)\right]$$

2.3.1 RESULTS

There exists a sequence $\{k_i\}$ such that $k_0 = \infty$, $k_i > 0$ for all $i \geq 1$, and $\lambda_i + \mu_{i+1} - \frac{\lambda_i \mu_i}{k_i} - k_{i+1} = y$ for all i≥0 for some constant y, if and only if $y \leq \gamma$[6].

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2.3.2RESULTS

For any constant c > 0, consider the sequence $\{K_i\}$ defined by

$k_1 = \lambda + g + h - c,\ c > 0,\ h \geq 0$

$$k_{i+1} = \lambda_{i+1} + \mu_i - \frac{\lambda_i \mu_i}{k_i} - c, i \geq 1 \qquad (2.1)$$

Let$l_i = k_i - \lambda_i$, $i \geq 1$ so$l_i$has the following recurrence relation:

$l_1 = h - c,\ c > 0,\ h \geq 0$

$$l_{i+1} = \frac{l_i}{\lambda_i + l_i}\mu_i - c, i \geq 1 \qquad (2.2)$$

Then $k_i > 0$ for all $I \geq 1$ if and only if $l_i > 0$ for all $I \geq 1$:

3. STEADY STATE AND TRANSIENT BEHAVIOR OF THE MODEL

In this paper we shall apply the results on both the steady – state and the transient behavior of the model of effects of PEG-GHRH. Since the mean GH output during the assessmentperiod of PEG-GHRH did not significantly differ from PEG-GHRH and GH stress values, therefore we shall assume

$h = 0$

Basic transient and steady – State properties for h = 0 (3.1)

The steady – state measure for x(t) [24] is

$$\pi_n = \frac{1}{\Gamma(g/\lambda)}\left(\frac{\lambda}{\mu}\right)^n \frac{\Gamma\left(n + g/\lambda\right)}{n!}$$

and $F(n) = \sum_{K=n}^{\infty} \frac{\pi_k}{S} = \frac{\pi_n F\left(n + g/\lambda, 1; n+1; \lambda/\mu\right)}{S}$, $n \geq 0$ [15]

In addition,

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$$S = \sum_{K=0}^{\infty} \pi_k = F\left(\frac{g}{\lambda}, 1; 1; \frac{\lambda}{\mu}\right)$$

$$= \left(1 - \frac{\lambda}{\mu}\right)^{-g/\lambda}$$

by the property of the hyper geometric function: $F(a, b; b; z) = (1-z)^{-a}$

This together with as $n \to \infty$,

$F(n) \cong \frac{1}{S} \frac{\Gamma\left(1 + h/\mu\right)}{\Gamma\left(g/\lambda\right)} \left(1 - \lambda/\mu\right)^{-1} \left(\lambda/\mu\right)^{n} n^{g/\lambda - h/\mu - 1}$ yields that

$$F(n) = \lim_{t \to \infty} P(X(t) \geq n) \cong \frac{1}{\Gamma\left(g/\lambda\right)} \left(1 - \frac{\lambda}{\mu}\right)^{g/\lambda - 1} \left(\frac{\lambda}{\mu}\right)^{n} n^{g/\lambda - 1} \qquad (3.2)$$

By $\eta(\theta) = \sum_{n=0}^{\infty} \frac{e^{\theta n} \pi_n}{S} = \frac{F\left(g/\lambda, 1; 1 + h/\mu; \left(\lambda/\mu\right)e^{\theta}\right)}{F\left(g/\lambda, 1; 1 + h/\mu; \lambda/\mu\right)}$,

The moment generating function of the steady–state distribution, under h = 0, is

$$\eta(\theta) = \left(\frac{\mu - \lambda e^{\theta}}{\mu - \lambda}\right)^{-g/\lambda}$$

Thus, for the steady – state distribution, the first two moments are [10]

$$m_1 = \eta'(0) = \frac{g}{\mu - \lambda} \qquad (3.3)$$

$$m_2 = \eta''(0) = \frac{g(\mu + g)}{(\mu - \lambda)^2}$$

and the variance is

$$m_2 - m_1^2 = \frac{(\mu g)}{(\mu - \lambda)^2}$$

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For the properties of the transient behavior [2], the decay parameter, which measures the speed of convergence to the steady state in an exponential way is given by γ = μ – λ

The transient mean and variance are $m_1(t) = ie^{(\lambda-\mu)t} + \frac{g}{\mu-\lambda}\left(1-e^{(\lambda-\mu)t}\right)$,

$$m_2(t) = i^2e^{2(\lambda-\mu)t} + i\,\frac{\lambda+\mu+2g}{\lambda-\mu}\left(e^{2(\lambda-\mu)t} - e^{(\lambda-\mu)t}\right)$$

$$+ \frac{g}{2(\mu-\gamma)}\left(1-e^{2(\lambda-\mu)t}\right) + \frac{g(\lambda+\mu+2g)}{2(\mu-\lambda)^2}\left(1-e^{(\lambda-\mu)t}\right)^2$$

The exponents in $m_1(t)$ and $m_2(t)$ are all related to λ- μ, which also points out, from a different viewpoint, that μ – λ should affect the speed of convergence in an exponential way[12]. In addition it is easily seen that

$$\lim_{t\to\infty} m_1(t) = \frac{g}{\mu-\lambda} = m_1$$

$$\lim_{t\to\infty} m_2(t) = \frac{g(\mu+g)}{(\mu-\lambda)^2} = m_2$$

3.1 RESULTS FOR MODEL- I

λ = 0.448 hyper secretion of PEG-GHRH

μ = 4.286 lower secretion of PEG-GHGRH (i.e.) λ<μ

If h=0 then decay parameter γ = 3.286 otherwise, if h>0 then

$\mu-\lambda \le \gamma < \mu-\lambda+h\left[1-\min\left(\frac{\lambda}{\mu}, \frac{\lambda+g}{\mu+h}\right)\right]$ The parameter g>0 models the rate of increase in X(t) due to non GH receptor factors. The parameter h attempts to capture the rate of decrease in x(t) due to GH receptor factors (ie) h=0, g=100.

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X axis Time (h)	**Y axis PEG-GHRH (ku/30min)**
2.1	λ_1 =24
2.5	λ_2=48
3.3	λ_3=72
4	λ_4=96
4.3	λ_5=120

X axis Time (h)	**Y axis GHRH (ku/30min)**
1.8	μ_1=336
2.9	μ_2=236
3.2	μ_3=36
3.9	μ_4=20

From result 2.3.2.

K_1=163.75	I_1=18.28
K_2=204.96	I_2=58.45
K_3=198.38	I_3= 112.25
K_4=238.25	I_4= 30.28
K_5=287.25	I_5=1.28

Thus d = 0, j = 1 and i $\rightarrow\infty$

$\lambda_i / \mu_i \geq \rho$: = 0.24

λ_1 / μ_1 = 3.625$\geq \rho$

λ_2 / μ_2 = 3.15 $\geq \rho$ etc.

If h = 0 then c< h(1-ρ) leads to a contradiction as c is assumed to be positive. If h>0 then γ<9.98 (ie) 3.286 ≤ γ < 9.98 [14].

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3.2 RESULTS FOR MODEL- II

For h = 0, the steady – state measure for X(t) is $Л_{12}$ = 9.2857 x 10^{-12} S = 1.4359 F(n) = 9.9 x $10^{-0.8}$

For the steady – state distribution under h = 0, the first two moments are

m_1 = 0.453

m_2 = 0.8359

and the variance is 0.732

The decay parameter γ = 3.286 should affect the speed of convergence is an exponential way[14].

4. DISCUSSION

The results of these two studies demonstrate that administration of PEG-GHRH generated a clear increase in circulating GH levels in both healthy young and healthy elderly subjects. There was, however, significant inter and intra – individual variation in response. The response appeared to plateau at higher doses, with no clear difference between the 2 mg and 4mg doses. This suggests not only a persistence of PEG-GHRH effect beyond the 24 – h dosing interval but also the absence of development of tolerance to this effect over the duration of this study. The findings of the repeated – dose study indicate a lasting capacity of the (possibly re-sensitized) pituitary to respond to GHRH stimulation. The effect of PEG-GHRH on the GH system is further supported by the sustained elevations observed in serum concentrations of both IGF-I and IGFBP-3.The levels of these mediators obtained after 6 days of PEG-GHRH administration in the elderly approached or even exceeded the mean levels observed in younger healthy subjects .IGF-I levels continued to increase and did not reach a steady state in the repeated-dose study. It would also be of interest to investigate the possibility that increasing serum IGF-I levels attenuate the effect of increasing the dose of PEG-GHRH through a negative feedbackmechanism. PEG-GHRH was well tolerated, with no medically significant AEs possibly related to treatment in

either study. Neither the frequency nor the severity of AEs appeared to be different from those following placebo, and there was no difference between the two doses on repeated administration. However, these reactions were transient and the local tolerability of PEG-GHRH was consideredacceptable. The time course of the response, as well as the serum level of GH and IGF-I obtained after only six subcutaneous injections, suggests that PEG-GHRH offers the possibility of less frequent dosing compared with GHRH.

5. CONCLUSION

A small difference in decay parameter can have a remarkable effect on the speed of convergence. The difference of decay parameter is large in PEG-GHRH.There is a significant inter and intra – individual variation in response. This suggests not only a persistence of PEG-GHRH effect beyond the 24 – h dosing interval but also the absence of development of tolerance to this effect over the duration of this study. The findings of the repeated – dose study indicate a lasting capacity of the (possibly re-sensitized) pituitary to respond to GHRH stimulation. Hence by the mathematical the decay parameter $\gamma = 3.286$ is large in the administration of PEG-GHRH. Hence GH had a marked and long-lasting effect on the administration of PEG-GHRH.

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