A NONLINEAR MATHEMATICAL MODEL OF AN IMMUNOTHERAPY TREATMENT OF PARATHYROID CARCINOMA

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Abstract: A mathematical model has been developed that describes the competitive binding process present in an immunotherapy treatment for parathyroid carcinoma. Compartmental analysis was employed to relate the flow and interaction of parathyroid hormone (PTH) and antibodies during the treatment. The model indicates a mechanism of how the antibody response effectively reduces the levels of free PTH. The results suggest that a maximum immune response occurs at approximately 13 weeks after the initial treatment. The immunotherapy treatment used injections of PTH hormone to induce an immune response; it was found that these injections had no negative effect on the PTH levels in the system. Additionally, the model allowed several conclusions to be drawn relating to optimal parameter choices with respect to treatment. For antibody binding the optimal level of effect was around $10^9 s^{-1}$, this is within the published *in vivo* range of 10^8-$10^{10} s^{-1}$. It was also established that the concentrations of parathyroid receptors are crucial in determining the pharmacodynamic effects of the treatment.

Keywords: Hypercalcemia, antibodies; parathyroid hormone; immunotherapy; compartmental models; nonlinear models; receptor binding kinetics.

1. INTRODUCTION

Parathyroid hormone (PTH) is a peptide hormone secreted by the parathyroid glands. It controls the concentration of calcium in the plasma by promoting intestinal absorption, renal reabsorption and release of calcium from the bones. Secretion of PTH from the glands is controlled by direct feedback from the concentration of calcium in the plasma. Parathyroid tumours are not common but overproduction of PTH by the tumours cause hypercalcaemia which, if untreated, can be fatal. A novel treatment for this condition was proposed by Bradwell and Harvey (1999) that utilized immunotherapy to affect a cure. The treatment used a combination of human and bovine PTH to force the patient's immune system to create antibodies (Ab) that would attach to PTH in plasma and prevent it from binding to PTH receptors (PTHr).

This paper proposes a mathematical model that describes the complex chemical interactions that take place during the auto-immune treatment described above. The model was simulated with published values to replicate possible treatment scenarios. The model facilitates understanding of the immunotherapy treatment, whilst also provid-

ing data on important features that may not be measurable by clinicians.

2. THE MODEL

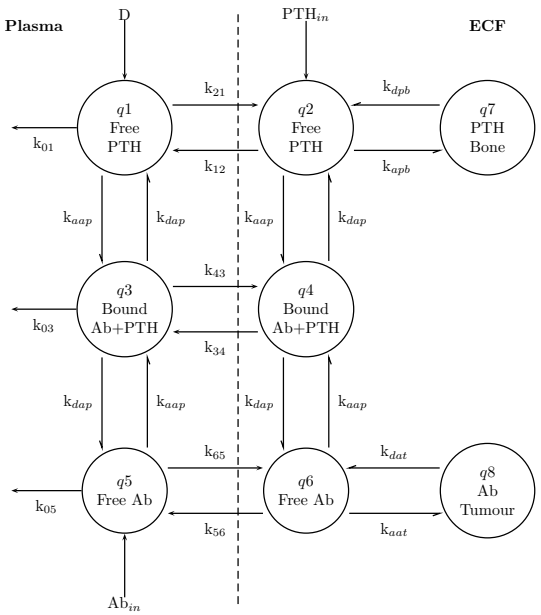

Fig. 1. Full Model containing PTH, Ab, PTH/Ab binding in plasma and ECF, including PTH and Ab tumour receptor binding

The model was developed using compartmental techniques, there are many excellent text books covering this subject (Godfrey, 1983; Jaquez, 1985). As can be seen in Figure 1 the compartmental model separates the process into three distinct components:

- PTH in plasma, ECF and bound to PTHr receptors.
- Bound PTH/Ab in plasma and ECF
- Ab in plasma, ECF and bound in close proximity to the PTH producing tumours.

This separation allowed the maximum use of available clinical data whilst maintaining an acceptable level of generalization.

The model incorporates the flow of material (free Ab, PTH and bound complexes of PTH/Ab) across the plasma/ECF membrane and the kinetic binding of the substances to receptors. It is assumed that no additional binding takes place and the flow of material across the plasma/ECF barrier is characterised solely by molecular size. In accordance with Thomas *et al.* (1989) PTH and Immunoglobulin G (IgG) molecules are able to pass freely between the two pools; whilst Immunoglobulin M (IgM), either free or bound, is unable to cross barrier. Due to the relative volumes of the two pools the rate constant of flow from ECF to plasma is considered to be approximately a fifth of that in plasma (Thomas *et al.*, 1989). In addition, the excretion rate of material is assumed to be equal to the flow from plasma to ECF as it is believed the substance must traverse the same biological path.

The reaction of Ab on PTH, and binding to relevant receptors, is modelled through simple binding kinetics (Foreman and Johansen, 2002). As shown in Chappell *et al.* (1991), if the receptor concentration is considered constant it is possible to remove the free receptor compartments from the model. This was possible in terms of PTHr and Ab tumour sites. However, as Ab and PTH is created and destroyed continuously the total number of receptors must be considered dynamic and therefore modelled as a compartment. The system of equations defining this model is given by:

$$
\begin{aligned}
\frac{\mathrm{d}q_1}{\mathrm{d}t} &= k_{dap}q_{3p} - k_{aap}q_1q_5 + k_{12}q_2 \\
&\quad - (k_{01} + k_{21})q_1 + D\delta(t) \\
\frac{\mathrm{d}q_2}{\mathrm{d}t} &= k_{dap}q_{4p} - k_{aap}q_2q_6 + k_{dpb}q_7 \\
&\quad - k_{apb}q_2[(C_{PTHRec} \cdot V_e) - q_7)] \\
&\quad - k_{12}q_2 + k_{21}q_1 + PTH_{in} \\
\frac{\mathrm{d}q_{3a}}{\mathrm{d}t} &= k_{aap}q_1q_5 - k_{dap}q_{3a} - q_{3a}k_{03} \\
&\quad - q_{3a}k_{43} + q_{4a}k_{34} \\
\frac{\mathrm{d}q_{3p}}{\mathrm{d}t} &= k_{aap}q_1q_5 - k_{dap}q_{3p} - q_{3p}k_{03} \\
&\quad - q_{3p}k_{43} + q_{4p}k_{34} \\
\frac{\mathrm{d}q_{4a}}{\mathrm{d}t} &= k_{dap}q_{4a} - k_{aap}q_1q_6 - q_{4a}k_{34} \\
&\quad + q_{3a}k_{43} \\
\frac{\mathrm{d}q_{4p}}{\mathrm{d}t} &= k_{dap}q_{4p} - k_{aap}q_1q_2 - q_{4p}k_{34} \\
&\quad + q_{3p}k_{43} \\
\frac{\mathrm{d}q_5}{\mathrm{d}t} &= k_{dap}q_{3a} - k_{aap}q_1q_5 + k_{56}q_6 \\
&\quad - (k_{05} + k_{65})q_5 + Ab_{in} \\
\frac{\mathrm{d}q_6}{\mathrm{d}t} &= k_{dap}q_{4a} - k_{aap}q_2q_6 + k_{dat}q_8 \\
&\quad - k_{aat}q_8[(C_{AbRec} \cdot V_t) - q_8] \\
&\quad - k_{56}q_6 + k_{65}q_5 \\
\frac{\mathrm{d}q_7}{\mathrm{d}t} &= k_{apb}q_2[(C_{AbRec} \cdot V_t) - q_7] - k_{dpb}q_7 \\
\frac{\mathrm{d}q_8}{\mathrm{d}t} &= k_{aat}q_6[(C_{PTHRec} \cdot V_e) - q_8]
\end{aligned}
\tag{1}
$$

$$
\begin{aligned}
y_1 &= c_1q_1 + c_3q_{3p} \\
y_2 &= c_5q_5
\end{aligned}
\tag{2}
$$

See Table 1 for a description of the variables and parameters. As can be seen above (eqn. 1),