Characterization of the pituitary response in the TRH test by kinetic modeling

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Abstract. Applying the principles of chemical kinetics to the time course of TSH concentrations after TRH infusion, individual values for total TSH release from the pituitary, TSH elimination and release rates, and latency for TSH release were found for 40 patients. Justification for using the observed peak TSH elevation as a consistent reflection of the total TSH release was provided by the high correlation between these two \( r = 0.97, P < 0.001 \). Kinetic modeling indicated that the most consistent reflection of total pituitary TSH response is the TSH elevation over baseline 35 min after TRH (with the peak expected 30 min post-TRH), rather than the area under the curve.

When are the best times to draw blood samples during the TRH test, and what are the physiological meanings of the blood TSH levels which result? Can the total response of the pituitary be well summarized by the peak elevation of TSH blood levels? If the answers to these questions were known, the TRH test could be performed more accurately and with fewer blood samples and thereby lower costs. The principles of chemical reaction kinetics (Levenspiel 1972) can be used to answer these questions.

Some other important clinical questions about the TRH test can be answered by the application of chemical kinetics:

1) How can we compensate for the effects of TSH elimination so that TSH concentrations at different times after TRH can be compared with each other, both across patients and for particular patients?

2) How does the area under the curve on a plot of the time course of the concentration of a response hormone (e.g., TSH) relate to the total amount of hormone released by the pituitary? With the TRH test this area has been presented as 'the most accurate measure of total TSH release' (Wilkin et al. 1979), but it is a mathematical truth that such equality between the area and the total hormone release is impossible because they have different physical units. The area has concentration-time units and the hormone release (per volume of distribution) has concentration units. Consequently, the conclusions of numerous studies which have assumed that this area represents the total hormone release are in doubt (e.g., Loosen et al. 1982; Schlesser et al. 1983; Whalley et al. 1984; Watabe et al. 1984).

3) How can an aberrant rate of TSH release (Casper & Frohman 1982) be characterized and expressed?

4) How much does the rate of TSH elimination vary among people?

The questions stated above bear directly on the details of the TRH testing procedures. The maxi-
Maximum elevation of TSH over baseline has been used as the outcome of the TRH test, in which a large bolus of TRH liberates all available TSH from the pituitary (Burger & Patel 1977; Casper & Frohman 1982; Extein et al. 1982; Lamberg & Gordin 1978; Loosen & Prange 1982; Utiger 1978; Winokur et al. 1983). Direct comparison (among patients) of TSH elevations at different times assumes that TSH elimination is negligible, while the rapid decline of TSH levels after its peak indicates otherwise. Another problem is that widely differing sampling methods are recommended to locate this peak (Extein et al. 1982; Lamberg & Gordin 1978; Loosen et al. 1982; Utiger 1978; Winokur et al. 1983).

Methods

1. Construction of the kinetic model

The more details of the course of concentrations that are described by a kinetic model, the larger the number of blood samples that are required. Even with the basic physiology of TSH release assumed as stated below, four blood samples are required. The terms P, R, E and L below are time constants to be determined for each course of TSH blood levels following a TRH infusion. There are four assumptions in the kinetic model:

1. TSH is removed from the blood at a rate proportional to its concentration; E is the elimination proportionality constant.

2. The process stimulating TSH release takes (full) effect at time L (min after TRH infusion) and decays in proportion to its intensity, with proportionality constant R. Thus, a larger R signifies more rapid completion of TSH release and an earlier TSH peak. The latency time L represents the delay between TRH and onset of consequent TSH release.

3. The homeostatic processes which kept TSH concentrations steady before TRH do not change enough following TRH to alter TSH levels. In other words, influences on TSH levels other than the TRH infusion can be accounted for by subtracting the baseline TSH level from post-TRH TSH levels.

4. The volume of TSH distribution (into a single body compartment) remains constant, so its mention will be omitted.

After integration the model can be written as:

\[ C = P \left( e^{-E(T - L)} - e^{-R(T - L)} \right) \]

where \( T = \) time since TRH infusion and \( C = \) elevation of TSH concentration over baseline; \( C = 0 \) before \( L \) min. The meaning of the coefficient \( P \) can be found by examining the hypothetical circumstance where TSH elimination has been entirely prevented (i.e., \( E = 0 \)) and TSH release has been completed (i.e., \( T = \) infinite). In this case the TSH concentration is steady and it is the total amount of TSH which can be released from the pituitary (per unit volume of TSH distribution); by the equation for this circumstance this concentration equals \( P \). In other words, \( P \) always represents the total amount of TSH released.

In contrast to coefficients derived from a polynomial representation of the TSH time course, which do not individually correspond to particular physiologic processes, each of the coefficients has a identifiable physiologic meaning. While the four coefficients can be determined with four TSH levels, particular TSH levels might be useless, e.g., one drawn during the latency period. Additional TSH levels might improve accuracy.

II. Evaluation of the model

It was expected that TSH patterns would vary widely among psychiatric inpatients (Loosen & Prange 1982; Winokur et al. 1983) and, so, allow us to observe how well the kinetic model would account for a wide range of TSH responses. Forty males under age 60 years were randomly selected. None had endocrine or organic brain disease; all were clinically euthyroid, with current normal total and free thyroxine levels. During the 4 months preceding testing none had abused alcohol or had taken lithium or other medications known to affect thyroid function. Informed consent was obtained prior to testing.

After an overnight fast, an iv catheter was placed at 09.30 h. Blood was collected at 10.00 h and 500 µg of synthetic TRH (Hoechst-Roussel) were infused over 15 sec. Samples were collected 15, 30, 45, 60, 90 and 120 min following TRH. TSH was assayed by radio-immunoassay kit (Clinical Assays, Inc., Cambridge, MA; C.V. 4.6%; sensitivity 2 mU/l).

The BMDP-PAR statistical package was used to fit the kinetic equation to the TSH levels. There are two different kinds of measures of the success of the procedure: the accuracy of the fit, and the certainty of the values of the coefficients which give the fit of highest accuracy. A 'unique best fit' is said to occur when the coefficient of variation of each coefficient is less than 100%; the alternative will be called a 'non-unique fit'.

A trial fitting which assumed the latency time \( L \) equalled zero led to numerical convergence for only 4 of the 58 sets of 5 or more TSH blood levels, indicating that the latency time \( L \) is not zero. After allowing \( L \) to vary, nearly all values of the elimination rate \( E \) fell between 0.01 and 0.02 min\(^{-1}\) (i.e., elimination half-life 35 to 70 min); \( E \) was then restricted to this range.

For most cases a unique best fit resulted; whenever there was no unique best fit, the coefficient of variation was largest for the release rate \( R \), indicating a shortage of detail of the rise in TSH levels. For cases with no unique best fit the latency \( L \) was set at 9.1 min, the
average of unique fits; this led to good uniqueness for most such cases.

There were thus four different ways in which coefficients were determined: 1) a straightforward unique best fit ('spontaneous unique'), 2) a unique best fit with limiting ranges placed on the coefficients ('constrained unique'), 3) 'non-unique' with the release rate R less than its standard deviation, and 4) 'defined determine' for the four sets which had included only four levels apiece. One case was excluded because its 1.2 mIU/l peak elevation was much smaller than all others.

Nineteen of the 57 time courses in the first three groups were repeated observations of the same patients; they were included because the repetitions were separated by at least 6 weeks, and the fit of a repetition did not tend to be in the same uniqueness group as the original. There were 78 possible pairings with other tests on the same patients; 25.6% were within the same group, not significantly different from the 35.9% expected by random assortment.

Results

The root mean square of the difference between observed and calculated levels, expressed as percent of peak elevation, was used to summarize the accuracy of the fit. This accuracy was comparable to the TSH assay coefficient of variation, and is listed in Table 1 along with average coefficients and correlation coefficients between total TSH release and peak elevation.

Peak TSH elevations averaged 8.9, 9.1, 12.9 and 9.0 mIU/l for the four groups, respectively; differences among these were not statistically significant. Total TSH release ranged from 45 to 64% larger than peak TSH elevation (average 55%).

The variability across patients was significantly larger for the total TSH release P than for the release rate R (P < 0.05) or the elimination rate E (P < 0.001), according to the statistical F-distribution. The coefficient of variation was 50% for total TSH release P, 32% for release rate R, 14% for elimination rate E, and 38% for latency L.

Discussion

The spontaneous unique group will be discussed; then other groups will be compared to it.

Justification for using the observed peak TSH elevation as a consistent reflection of the total TSH release is provided by the near-perfect correlation (r = +0.97) between them; the former is 61% as large as the latter. The 94% overlap in variance between the peak and the total release contrasts with the 42% overlap in variance for a similar analysis of prolactin release after seizure reported elsewhere (Swartz 1985); this is probably because prolactin is released and eliminated much more rapidly than TSH. TSH elimination effects are remarkably large, since 39% of the TSH released by the time of the peak had already been eliminated, on average.

The peak occurs at time L + ln(E/R)/(E − R) after TRH (average 29.6, SD 4.5 min). Sampling for the peak at the average time of its occurrence predisposes to a great underestimation of it for patients whose latency time is above average or whose release rate is slower than average. This is because TSH levels change more rapidly before the peak than afterwards. According to the kinetic

<table>
<thead>
<tr>
<th>Type of fit</th>
<th>N</th>
<th>Fit</th>
<th>Total TSH release P (mIU/l)</th>
<th>Release rate R (min⁻¹)</th>
<th>Elimination rate E (min⁻¹)</th>
<th>Latency L (min)</th>
<th>Total release (P) to peak TSH elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unique</td>
<td>20</td>
<td>2.1%</td>
<td>13.7</td>
<td>0.129</td>
<td>0.014</td>
<td>9.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Constrained unique</td>
<td>25</td>
<td>5.1%</td>
<td>13.4</td>
<td>0.155</td>
<td>0.014</td>
<td>9.3</td>
<td>0.92</td>
</tr>
<tr>
<td>Non-unique</td>
<td>12</td>
<td>4.5%</td>
<td>23.1</td>
<td>0.091</td>
<td>0.017</td>
<td>10.1</td>
<td>0.95</td>
</tr>
<tr>
<td>Defined determinate</td>
<td>4</td>
<td>—</td>
<td>17.8</td>
<td>0.068</td>
<td>0.014</td>
<td>9.0</td>
<td>—</td>
</tr>
</tbody>
</table>

The significance of each correlation r was P < 10⁻⁵.
model, sampling 35 min after TRH gives a narrower range for the TSH level (90.8–99.7% of peak levels) than does sampling at the average peak time of 30 min (86.4–100% of peak levels); yet, the TSH elevations expected are about the same (97.9 vs 96.8%, respectively). Since the elimination half-life (49.5 min) varied little among patients, drawing more than one TSH blood level after the peak adds nothing more than duplication.

The average latency of the TSH response to TRH was 9.1 min (SD 3.7 min). Earlier details of TSH release are not in the model (and would of course necessitate additional blood levels). The short time for half-completion of TSH release (5.4 min) indicates that release concludes by 25 min after latency, just after the peak.

Since both latency and release rate are highly variable, a single TSH level prior to the peak (i.e., during the first 20 min) is not sufficient to represent the course of rising levels precisely. Two levels before the peak and after latency are required, plus one slightly after the peak to determine total TSH release. The correlation of \( r = +0.37 \) (\( P < 0.05 \)) which occurred between the release rate \( R \) and the latency time \( L \) is probably an artefact of the numerical procedure operating on a suboptimal schedule of blood sampling. With the hindsight of the present results, optimal times for the two blood samplings to describe latency and release are 12.2 and 17.6 min, the average times for one-third and two-thirds of total TSH release to occur, respectively; Fig. 1 illustrates this. With delayed TSH release (Casper & Frohman 1982) the course may be best characterized with levels at 15, 22.5, 45 and 90 min.

Since the TSH elimination rate \( E \) of 0.014 min\(^{-1}\) varied little among patients, and this rate is the dominant influence on the shape of the time

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**Table 2.**

Corrections to multiply TSH levels by for various times after TRH.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>re: 30 min TSH level</th>
<th>re: total TSH release</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.0</td>
<td>1</td>
<td>1.473</td>
</tr>
<tr>
<td>35.0</td>
<td>1.028</td>
<td>1.514</td>
</tr>
<tr>
<td>45.0</td>
<td>1.140</td>
<td>1.680</td>
</tr>
<tr>
<td>60.0</td>
<td>1.388</td>
<td>2.045</td>
</tr>
<tr>
<td>90.0</td>
<td>2.107</td>
<td>3.104</td>
</tr>
</tbody>
</table>
course after the peak, the average values for the coefficients can be applied to compensate for the effects of elimination on TSH levels which occur 30 min or more after TRH. This correction permits the comparison of TSH levels at different times without individualized kinetic modeling. Table 2 presents multiplication factors for conversion of a TSH level to the equivalent 30 min level and the corresponding total release level; e.g., multiply a 45-min level by 1.14 for comparison with a 30-min level. While these correction factors are approximations they should be more accurate than not making a correction.

If additional samples had been taken during the TSH rise, the spontaneous unique group should have been much larger. Inaccuracy does not follow lack of uniqueness; among non-unique fits accuracy was within 0.6 and 0.8% in two cases, better than the spontaneous uniques' average.

Coefficients for the constrained unique group are near those of the spontaneous unique group, suggesting that the constraints were realistic. Nothing besides non-uniqueness distinguished the non-unique group: there was an even spread of peak elevations within this group from 2.8 to 38.4 mIU/l. While these peaks were not significantly larger than other groups, they included the three largest (38.4, 31.3 and 23.3 mIU/l); although the three corresponding patients had normal thyroid hormone levels they are presumably borderline hypothyroid.

A model mathematically similar to the present one, but without allowing latency, was previously described (Saratchandran et al. 1976); uniqueness of the fit, implications for the TRH test, and clinical applications were not discussed.

The area under the response hormone elevation vs time curve is not the total amount of hormone released, which some authors have mistaken it to be (Loosen et al. 1982; Schlesser et al. 1983; Watabe et al. 1984; Whalley et al. 1984; Wilkin et al. 1979). Rather, for the TRH test, this area is the cumulative body exposure to the TSH released by TRH, which is a stimulus for hormone release from the thyroid and may itself have application to clinical testing (Shenkman et al. 1972). That this area does not necessarily represent the pituitary response is illustrated by a hypothetical case in which a pharmacologic agent which prevents TSH elimination is given prior to TRH infusion; in this example if there is any TSH release the area under the curve will be infinite.

From the model the area under the curve is explicitly expressed by (P/E - P/R), which depends on the rates of elimination and release and so does not consistently represent total TSH release. Because the elimination rate E is relatively constant among patients and P/E is about ten times the size of P/R (see Table 1), this area tends to be proportional to the total TSH release P, which explains the reported correlation between this area and peak TSH elevation (Schlesser et al. 1983).

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References


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