A SIMPLE CLINICAL METHOD FOR ESTIMATING THYROXINE SECRETION RATE

By

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ABSTRACT

A simple method for measuring thyroxine secretion rate (T₄SR), suitable for use in routine clinical practice, is presented. T₄SR equals 4.6 times the inverse of the plasma specific activity on the seventh day after administration of a single tracer dose of radiothyroxine. Data indicating the reliability of the method are presented and the theoretical basis is fully discussed. A detailed procedure is provided.

In clinical medicine simple tests of thyroid function, such as the concentration of plasma Protein Bound Iodine (PBI), sometimes fail to provide a diagnosis and can even be misleading. For example, administration of oral contraceptives, salicylates or diphenylhydantoin can cause abnormal levels of PBI due to alteration in the specific plasma binding proteins (Osorio 1967). Various methods for estimating plasma «free-thyroxine» can help in these cases (Clark 1967), but an increasing number of situations have been described where these indices fail to give a true indication of thyroid status (Oppenheimer 1968; Harland & Orr 1969a). There is therefore a need for a simple method of estimating the daily output from the thyroid gland directly.

The real basis of the euthyroid state is correct balance between the supply and demand for thyroid hormones. It is not yet possible to quantitate demand, but reliable methods are available for estimating the rate of secretion of thyroxine (T₄SR). The most direct of these is based on the disappearance of a tracer dose of radiothyroxine from the plasma, and this method has often been applied in experimental medicine since its introduction by Ingbar & Freinkel (1955). However, the method has not been widely accepted because of its complexity and the
large number of blood samples required. There is also the theoretical objection that the method assumes that thyroxine leaves the plasma at a single exponential rate which, in our experience, is not always the case. In this event $T_4$SR can be more correctly estimated by some form of compartmental analysis (Sharney et al. 1965) or more simply by the method of Harland & Orr (1969b).

Recently, Jubiz et al. (1969) introduced a new semi-empirical test of thyroid function using a single blood sample to determine the plasma thyroid specific activity three days after administration of radiothyroxine. This test was shown to give good discrimination between normal and abnormal thyroid conditions. The purpose of this paper is to present and explain an extension of their method which provides a simple and reliable clinical method of estimating $T_4$SR.

**METHOD**

$T_4$SR and Plasma Specific Activity

The three methods mentioned above for estimating $T_4$SR all have the same basic form, which is true whatever abnormalities there may be in binding or turnover rate, or indeed whatever model of thyroxine metabolism is envisaged (Orr & Gillespie 1968).

$$T_4SR = \frac{T_4 \text{ concentration in plasma}}{\text{Area under plasma fractional radioactivity concentration curve}}$$  (1)

Jubiz et al. (1969) suggested using the plasma thyroxine specific activity on the third day after the injection of radiothyroxine as an index of thyroid status. The relationship they established is equivalent to a correlation between $T_4$SR and the inverse of the plasma thyroxine specific activity, i.e.

$$T_4SR \propto \frac{T_4 \text{ concentration in plasma}}{\text{Plasma fractional radioactivity concentration on day three}}$$  (2)

The similarity of the two expressions (1) and (2) suggests that the plasma radioactivity on day three should correlate with the area under the plasma radioactivity curve, whatever the slope of the curve may be. This is illustrated in Fig. 1.

It appeared to us on theoretical grounds (see below), that day three would not be the best time to measure specific activity. To test whether day three gave the best correlation in practice we took as an example the data on patients studied by Ingbar & Freinkel (1955). The coefficients of correlation between fractional activity on each day and the total area were calculated. The results are shown in Table 1, where it can be seen that the correlation improves steadily up to day eight and then declines, but changes little between days six and nine. Similar results were found for the correlations between activities and total areas for fourteen Glasgow patients whose $T_4$SR had been measured by the method of Harland & Orr (1969b). The mean half lives of radiothyroxine in these patients varied from 2.5 to 10 days. It is concluded that the optimum time for measuring plasma specific activity in clinical practice is day seven, rather than day three as suggested by Jubiz et al. (1969).

To illustrate the good correlation and the direct proportionality obtained, the $T_4$SR for the Glasgow patients plotted against the inverse of the plasma specific activity on day seven is shown in Fig. 2. Plasma activity is expressed as a percentage of dose.
An illustration of the relationship between plasma activity on different days and the total area under the plasma activity - time curve (t½ approximately 10 days).

![Graph showing plasma radioactivity vs days](image)

**Fig. 1.**

**Table 1.**

Correlation between plasma activity on succeeding days after radiothyroxine and the total area under the plasma activity - time curve.

<table>
<thead>
<tr>
<th>Day</th>
<th>Coefficient of Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.874</td>
</tr>
<tr>
<td>4</td>
<td>0.929</td>
</tr>
<tr>
<td>5</td>
<td>0.966</td>
</tr>
<tr>
<td>6</td>
<td>0.972</td>
</tr>
<tr>
<td>7</td>
<td>0.974</td>
</tr>
<tr>
<td>8</td>
<td>0.975</td>
</tr>
<tr>
<td>9</td>
<td>0.974</td>
</tr>
</tbody>
</table>

A moderate correlation, at least, is to be expected for the data in Fig. 2, since both axes contain the PBI, as a factor. The correlation coefficient between T₄SR and PBI is however, only 0.606, whereas the correlation coefficient between T₄SR and inverse specific activity is 0.986. Fig. 2 also indicates that for the line of best fit the T₄SR is equal to 4.6 times the inverse specific percentage activity.

**Theory**

For simplicity the theory will be confined to consideration of a mean half life (T½) of the radiothyroxine disappearance curve, corresponding to a fractional disappearance rate, k, where $k = \frac{1}{T_{1/2}} = \frac{0.693}{T_{1/2}}$. The plasma radioactivity
Inverse of plasma specific activity measured on day 7 plotted against T₄SR. The regression equation and coefficient of correlation (r) are shown.

Concentration, expressed as a fraction of dose, will be denoted by \( h \) with a subscript indicating the day of measurement.

Then,

\[
\text{Total area under radiothyroxine curve} = \frac{h_0}{k}
\]

But since,

\[
h_0 = h_t \times e^{kt},
\]

\[
\text{Area} = \frac{h_t \times e^{kt}}{k}
\]

\[
\cdots \frac{\text{Area}}{h_t} = \frac{e^{kt}}{k}
\]

Now, if area and \( h_t \) are to correlate closely, the ratio \( \frac{e^{kt}}{k} \) must be almost constant. Fig. 3 shows a plot of \( \frac{e^{kt}}{k} \) against \( k \) for two values of \( t \) (days 3 and 7). It is clear that, over the range of values of \( k \) observed in clinical practice (0.075–0.25), this is almost constant for day seven. There is more variation for day three, the change being particularly significant with the low rates of disappearance such as occur in myxoedema. It follows that the T₄SR can be expected to correlate more closely with the specific activity at day seven than with that at day three.
The function \( \frac{e^{kt}}{k} \) plotted against fractional disappearance rate (k) for \( t = 7 \) and \( t = 3 \). The range of k encountered clinically is indicated by the bar. The proportional change in the value of the function over this range is considerably greater for day 3 than day 7.

**DISCUSSION**

The theoretical considerations above indicate that the inverse of plasma specific activity on the seventh day after a dose of radiothyroxine should be proportional to the T₄SR, over the whole range of thyroxine disappearance rates found in clinical practice. The data presented in Fig. 2 show that this correlation is indeed very close. It should be noted that the correlation holds in all cases, even those where the PBI failed to give a true indication of thyroid activity. The data also show that T₄SR is 4.6 times the inverse of the specific activity on day seven.

This method of estimating T₄SR is as simple as it is accurate. Only a single blood sample is required, and this eliminates the chief objection to the use in routine clinical practice of the established methods for T₄SR. The method can also be applied for measurement of T₄SR in experimental animals, but in each species the optimum time at which specific activity is measured and the appropriate factor will be different. These can be found by a similar procedure to that discussed in the theory.

**PROCEDURE**

A suitable procedure for carrying out the test is as follows. Radiothyroxine (5–10 \( \mu \text{Ci} \)) is given intravenously in 50 % propylene glycol after sterilization by
millipore filtration. Radiothyroxine labelled with either $^{131}$I or $^{125}$I can be used, but the latter is generally to be recommended because of greater stability and consequently less contaminating radioiodide. At the time of injection a standard is prepared by placing a dose in a volumetric flask containing 2 N NaOH to prevent adherence of the label to the glass.

One week later a blood sample is withdrawn and the plasma activity measured and expressed as per cent dose per litre. Plasma thyroxine concentration per litre is measured on the same sample. If direct $T_4$ estimations are not available the PBI ($\mu g$ $l/l$) gives a reasonable approximation. Then

$$T_4SR = \frac{\text{Plasma } T_4 \ (\mu g/l)}{\text{Plasma activity } (\% \text{ dose}/l)} \times 4.6.$$ 

REFERENCES


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