Serum Prolactin Responses to TRH in Recurrent Breast Cancer Patients

Michio Miyazaki
Kazuhiko Yasumura, Satoshi II, Yasuaki Takata and Toshiaki Kami

Department of Surgery, Nippon Kokan Hospital
Kawasaki 210, Japan

Synopsis

The response of serum prolactin (PRL) to thyrotropin-releasing hormone (TRH) was evaluated by radioimmunoassay in 6 normal women and 44 breast cancer cases. They were divided into the following 5 groups: group 1: 6 normal women; group 2: 10 preoperative patients with early breast cancer; group 3: 13 preoperative patients with advanced cancer; group 4: 13 postoperative patients with no recurrence of cancer for more than 2 years; group 5: 8 postoperative patients with cancer recurrence.

The maximum increment of serum PRL levels following the administration of TRH was significantly higher in groups 2, 3 and 5 than in groups 1 and 4. These results indicate that patients with recurrent breast cancer have a higher PRL response to TRH than those without recurrence of cancer.

The relationship between pituitary gland function and breast cancer has been recognized since first suggested by Gomez and Turner (1937). There have now been numerous studies (MacMahon et al., 1973; Minton, 1974; Smithline et al., 1975; Hill et al., 1976; Kirschner, 1977; Nagasawa, 1978) on the role of prolactin (PRL) in human breast cancer. Some investigators (Murray, 1972; Rolandi et al., 1974) have found that the blood PRL levels in breast cancer patients are higher than the levels in normal subjects, but others (Boyns et al., 1973; Sheth et al., 1975) have found no significant increase in PRL levels in their patients.

There have also been several receptors on the kinetics of PRL, including its response to thyrotropin releasing hormone (TRH) in patients with breast cancer, (Mitra et al., 1974; Ohgo et al., 1976; Endo et al., 1977; Higuchi et al., 1977) but none state unequivocal findings. No studies have yet clearly elucidated the relation between PRL response to TRH and recurrence of breast cancer.

In this study a comparison was made between patients with and without recurrence of breast cancer with respect to PRL response to TRH.

Materials and Methods

Serum PRL responses to TRH were assessed and compared in a series of 50 women divided into 5 groups, i.e. group 1: 6 normal women; group 2: 10 preoperative patients with early or incipient breast cancer (Stage I by the new TNM classification); group 3: 13 preoperative patients with advanced breast cancer (Stage II, III or IV); group 4: 13 postoperative patients without recurrence of cancer for more than 2 years; group 5: 8 postoperative patients with recurrent cancer.

Received April 8, 1978.
There were 8 postmenopausal breast cancer patients and 36 premenopausal breast cancer patients. Three postmenopausal cases occurred in group 2, 1 in group 3, 1 in group 4 and 3 in group 5.

The response of PRL release to exogenously administered synthetic TRH was studied in all groups. All patients were admitted to the hospital for the study and in the case of premenopausal women, the studies were done immediately after the menstruation. Blood samples were taken after an overnight fast at 6:00 a.m. on the day of testing and 15, 30, 60 and 120 min later following the intravenous administration of 500 μg of synthetic TRH (Tanabe Co., Osaka, Japan).

Serum PRL and thyroid-stimulating hormone (TSH) were determined by double antibody radioimmunoassay methods, using PRL and TSH kits (Daiichi Radioisotope Lab., Tokyo, Japan). In addition, sera of all cases were assayed (Masuoka and Mimoto, 1978) for detection of human thyroglobulin antibody (Sorin, Saluggia, Italy).

To investigate the degree of response of serum PRL and TSH to TRH we calculated the mean maximum increment above the basal level (max ΔPRL and max ΔTSH) by measuring peak PRL or TSH value after administration of TRH minus basal PRL or TSH value.

Statistical analysis of PRL and TSH values between these groups was performed by the Student's t-test and linear regression analysis was done by the method of least squares.

Results

Prolactin

No significant differences were observed between any two groups in the basal level of serum PRL. Fig. 1 shows the time course of the serum PRL levels after administration of TRH. In all groups the PRL value reached its peak after 15 or 30 minutes following TRH injection and declined gradually thereafter. The max ΔPRLs of groups 2, 3 and 5 were significantly higher than those of groups 1 and 4. But no significant differences were

Fig. 1. Serum prolactin responses to TRH in 5 groups. Note that serum PRL levels peaked at 15 or 30 min in all groups and groups 1 and 4 are alike in response pattern and groups 2, 3 and 5 are also similar to each other in this respect.
found between any other two groups. The max ΔPRL of 6 preoperative non-advanced breast cancer patients in group 2 was not significantly different from those in group 1 and 4, although the mean max ΔPRL of group 2 was elevated due to high max PRLs found in the four patients in this group who underwent breast biopsy.

**Thyroid-stimulating hormone**

There were no significant differences in the mean response to TRH between the 5 different groups and no correlations were observed between the basal levels of TSH and PRL or in their response to TRH.

**Thyroglobulin antibody**

We detected circulating thyroglobulin antibody in 4 postoperative patients without recurrence (group 4) but none in any patients from other groups. All PRL values of these 4 patients were approximate to the mean value of the group. Their TSH values were higher than those of other patients but not statistically significant.

**Discussion**

As Welsch and Nagasawa (1977) detailed, in recent years, a large body of experimental data has been accumulated demonstrating a key role for PRL in the development and growth of murine mammary tumors. Although there have been some reports that the blood PRL concentrations of breast cancer patients are higher than those of normal subjects (Murray et al., 1972; Rolandi et al., 1974), most studies to date have found the blood PRL concentrations to be within the normal range (Boyns et al., 1973; Franks et al., 1974; Kwa et al., 1974; Sheth et al., 1975).

Kirschner (1977) has pointed out that PRL levels in blood are quite labile and fluctuate greatly, thus making single determinations of this hormone of little value. Thus the temporal response of serum PRL to TRH is very useful in the evaluation of pituitary PRL secretion in human subjects and the maximum increase in serum PRL above the base line level has been used as an index of response (Jacobs et al., 1973).

Mitra et al. (1944) reported that in their studies there were no statistical differences in the mean basal PRL levels between three groups (early breast cancer, advanced breast cancer and normal control). However, only women with advanced breast cancer exhibited a marginally greater pituitary reserve of PRL as evidenced by

<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>max ΔPRL Mean ± S.E. ng/ml</th>
<th>Significance</th>
<th>max ΔTSH Mean ± S.E. µU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normal control</td>
<td>6</td>
<td>95.6 ± 23.2</td>
<td>2*, 2*, 5**</td>
<td>26.8 ± 13.6</td>
</tr>
<tr>
<td>2. Preoperative non-advanced cancer</td>
<td>10</td>
<td>242.9 ± 40.8</td>
<td>1*, 4***</td>
<td>18.4 ± 2.7</td>
</tr>
<tr>
<td>3. Preoperative advanced cancer</td>
<td>13</td>
<td>230.5 ± 35.8</td>
<td>1*, 4***</td>
<td>25.3 ± 10.7</td>
</tr>
<tr>
<td>4. Postoperative non-recurrent cancer</td>
<td>13</td>
<td>107.3 ± 15.2</td>
<td>2***, 3***, 5***</td>
<td>23.9 ± 3.3</td>
</tr>
<tr>
<td>5. Postoperative recurrent cancer</td>
<td>8</td>
<td>252.1 ± 42.8</td>
<td>1***, 4***</td>
<td>29.0 ± 8.8</td>
</tr>
</tbody>
</table>

*: P<0.05  **: P<0.02  ***: P<0.005
There were no significant differences between max ΔTSH of 5 different groups.

cf. In group 2 six preoperative non-advanced cancer patients (except 4 biopsied patients) did not differ from any other groups. (max. ΔPRL: 192.7 ± 51.9)
a significantly higher plasma level of this hormone in response to TRH stimulation. Ohgo et al. (1976) did not find any significant difference in the mean response of plasma PRL following TRH injection in patients with breast cancer compared with that in normal subjects. However, they demonstrated that some patients with breast cancer had apparently increased basal plasma PRL levels and showed exaggerated responses of PRL to TRH. Higuchi et al. (1977) failed to detect any significant correlation between the serum PRL concentrations (both the basal levels and the responses to TRH) and the stage in TNM classification, or the histological picture of breast cancer. Endo et al. (1977) recognized that the PRL responses to TRH in cases of ulcerated breast cancer and cases of biopsied breast cancer were significantly different from those in normal subjects.

Although Franks et al. (1974) reported that the basal PRL levels in premenopausal breast cancer patients are higher than those in postmenopausal patients, in our study there were no significant differences in either basal levels or the response to TRH between pre- and post-menopausal patients.

Yamaji (1974) reported that TRH-mediated PRL release was enhanced in most cases of primary hypo-thyroidism, so we examined the TSH response to TRH, and thyroglobulin antibody in all cases. There were no significant differences in the TRH response to TRH between the groups and no correlations between max ΔTSH and max ΔPRL in all cases, and the PRL values of patients who had thyroglobulin antibody were similar to the mean value of the group. Therefore, we can exclude the possible causal relationship between cases with hypothyroidism or chronic thyroiditis, and our present cases with enhanced PRL responses to TRH.

We demonstrated that the max ΔPRL in recurrent breast cancer patients was higher than in postoperative breast cancer patients without recurrence, which has not been previously reported. There are two possible interpretations of these results: (1) the preoperative patient with a high PRL response to TRH is apt to suffer from recurrence of breast cancer, or (2) the postoperative high PRL response to TRH results from recurrent breast cancer. Regarding the first interpretation, as the degree of max ΔPRL in preoperative breast cancer patients was variable, if the patients (group 2 and 3) with high max ΔPRL fell into the recurrent group (group 5) after operation and those with low max ΔPRL fell into the non-recurrent group (group 4), this hypothesis would be confirmed. If this turns out to be true, then we will propose that the PRL response to TRH may be used as an index of recurrence of breast cancer.

The 4 biopsied breast cancer patients were included in the preoperative non-advanced cancer group (group 2). Their PRL responses to TRH were high by confirming the report of Endo et al. (1977). There were no significant differences between the mean max ΔPRL in this group except these biopsied patients and those in other low PRL groups. We do not know why the biopsy procedure enhanced the PRL responses to TRH.

As the recurrence of breast cancer is dependent not only on PRL but also on other factors, any conclusions regarding the relationship between PRL response and recurrence of breast cancer must be drawn only after the long term follow up of many patients, especially preoperative patients (groups 2 and 3). Further studies should be made to report the status of preoperative advanced and non-advanced breast cancer patients after several years.
Acknowledgements

The authors thank Dr. T. Amaaki (director of Nippon Kokan Hospital), Dr. K. Tokunaga and Dr. T. Muraki (Department of Pharmacology, Keio University) and also Dr. T. Makino (Department of Gynecology, Keio University) for their kind instruction during this work. Thanks are also due to Miss Y. Masuda for her technical assistance.

References


