EFFECTS OF THYROTROPIN-RELEASING HORMONE IN SCHIZOPHRENIA

KAZUTOYO INANAGA, TETSUO NAKANO AND TOSHIYASU NAGATA

*Department of Neuropsychiatry, Kurume University School of Medicine,
Kurume, 830, Japan*

MASATOSHI TANAKA

*Institute of Brain Diseases, Kurume University School of Medicine,
Kurume, 830, Japan*

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A clinical appraisal was made of thyrotropin-releasing hormone (TRH) used in combination with psychoactive drugs in schizophrenia. The results obtained may be summarized as follows:

1. In conjunction with maintenance neuroleptics therapy, TRH, 4 mg daily, was administered for 14 days to 62 schizophrenics, including 32 males and 30 females, who exhibited reduced spontaneity, abulia, apathy and autism (social withdrawal) as principal symptoms. Those who had psychomotor excitement or marked hallucinations or delusions were excluded.

2. Of the 62 patients treated, 27 (43.5%) responded excellently or well and 46 (74.1%) to a more or less favorable extent. Symptomatic aggravation resulted in 6 (9.6%) and no symptomatic response was elicited in 10 cases (16.1%). Facial expression, rapport and physical activity were outstanding among features that responded favorably to the hormone.

3. No substantial difference existed between types of the illness in regard to the effectiveness of the hormone. Symptomatic aggravation was more frequent in females than males. Fair or better responses tended to be of higher incidence among patients institutionalized for 5 years or more than among those for shorter periods. The effect of the hormone was manifested within a week, and lasted for a variable period in different cases. Adverse effects were observed in 1 out of 62 cases.

Wilson and associates⁶⁾ reported that normal women, when infused intravenously with thyrotropin-releasing hormone (TRH), become relaxed with mild euphoria and a sense of increased energy. In a study on the effect of intravenous TRH in 4 schizophrenics these investigators⁷⁾ further stated that there was regaining of emotional warmth, lucidity

of thought and accessibility of psychotherapy a few hours after the initial dose of TRH to these patients with schizophrenia.

Inanaga et al.⁵⁾ found psychic symptoms and signs markedly improved in 3 out of 5 schizophrenics treated with a combination of TRH and neuroleptics. These 3 patients had improved rapport

while becoming less gloomy in facial expression and more active in behavior in general. Encouraged by such a pronounced response in some documented instances, we have made a trial of TRH used in combination with psychotropic drugs to assess its benefit in 62 patients with schizophrenia. The results obtained are presented below.

METHODS

Subjects

Our series consisted of inpatients with schizophrenia at the Neuropsychiatric Service, Kurume University Hospital or affiliated institutions, who presented with loss of initiative, abulia, apathy and autism (social withdrawal) as principal symptoms. Patients who had severe psychomotor excitement or prominent hallucinations or delusions were excluded, as were those who were suspected of having thyroid dysfunction. There were 32 males and 30 females included in this study, their age ranging from 19-54 years with a mean of 32.8 years.

Methods

In addition to the preceding therapy with neuroleptics and anticholinergics, a preparation containing 2 mg of TRH in each tablet was administered per os in daily dose of 4 mg or 2 tablets b. i. d. in the morning and at noon or in the morning and evening. Treatment lasted 14 days as a rule.

In describing the response of presenting symptoms and signs, no specific rating scale was employed but care was taken to express their changes in as concrete terms as possible.

Overall appraisal of the effectiveness of the hormone was made according to the following criteria :

Excellent :

Principal symptoms responded so satisfactorily as to warrant discharge or rehabilitation of the patient.

Good :

Principal symptoms subsided distinctly with the resultant increased adaptability to hospital life.

Fair :

Partial symptomatic relief accomplished.

Poor :

Principal symptoms remained unaltered or were altered both partially and variably.

Aggravated :

Principal symptoms aggravated either partially or entirely.

For statistic analyses of the results, the chi-square test or Fisher's exact probability test was employed.

RESULTS

1. Effectiveness of TRH in relation to the types of illness

The overall effectiveness of TRH in different types of schizophrenia is summarized in Table 1. No valid comparison of the paranoid and other types with the hebephrenic or catatonic type can be made because of the limited number of cases in the former groups. Comparing the latter 2 types, it appears that favorable responses were somewhat more frequent for the catatonic than the hebephrenic type, an excellent or good response being educed in 13 (34.2%) of 38 cases of the latter type as compared with 9 (50%) of 18 cases of the former. Statistic verification, however, disclosed no significant difference between the 2 types. The frequency of more or less favorable responses was much the same for both types : 28 (73.6%) of

TABLE 1
Effectiveness of TRH in relation to the types of illness

Overall effectiveness Clinical types	Excellent	Good	Fair	Poor	Aggravated	Total
Hebephrenic type	7	6	15	8	2	38
Catatonic type	4	5	4	1	4	18
Paranoid type	2	1				3
Others	1	1		1		3
Total	14	13	19	10	6	62

38 cases of the hebephrenic type and 13 (72.2%) of 18 cases of the catatonic type. Obviously, there was no statistically significant difference between the types in this regard. Symptomatic aggravation ensued somewhat more frequently in cases of the catatonic than the hebephrenic type: 4 of 18 cases of the former and 2 of 38 cases of the latter. Such a tendency was substantiated on statistic grounds as well ($p=0.066$). Of the entire series of 62 cases, 27 (43.5%) responded either excellently or well and 46 (74.1%) to a more or less favorable extent.

2. *Effectiveness of TRH in relation to separate symptoms*

Facial expression, rapport and physical activity of the patient were the features in which prominent symptomatic relief was attained. Impressive changes that took place include "talking face to face with others now in contrast to the previous drooping and mutism", "having become inclined to talk to others", "being not confined to the bed any more but televiewing or participating in recreational programs" and so forth. Those patients who had abnormal experiences such as hallucinations or delusions or who presented with such symptoms as inappropriate laughter, monologue, wandering or extremely stiffened facial expression were

often found falling into the categories "poor" or "aggravated". In some of the patients who had mildly abnormal experiences along with loss of spontaneity, abulia and autism (social withdrawal) as predominant symptoms, such experiences subsided in parallel with a favorable response being elicited in terms of facial expression, rapport and physical activity.

Of the patients who had symptoms or signs manifested as an adverse reaction to TRH, 3 became violent towards others while in excitement; 2 complained of morbid experiences or depersonalization; 2 had insomnia; 1 tended to refuse to take food or drugs; 1 had increased appetite; and 1 became more hypochondriacal.

3. *Effectiveness of TRH in relation to the sex of subjects*

The overall effectiveness of TRH in different sex groups is shown in Table 2. The incidence of an excellent or good response was much the same for both sexes: 14 (43.7%) of 32 males and 13 (43.3%) of 30 females. It appears that more or less favorable responses were somewhat more common among males than females, the incidence being 81.2% or 26 of 32 cases for the former as compared with 66.6% or 20 of 30 cases for the latter. There was no statistical-

TABLE 2
Effectiveness of TRH in relation to the sex of subjects

Overall effectiveness Sex	Excellent	Good	Fair	Poor	Aggravated	Total
Male	6	8	12	5	1	32
Female	8	5	7	5	5	30
Total	14	13	19	10	6	62

ly significant difference between sexes, however, as to either the incidence of good or better responses or that of fair or better responses. Adverse responses to TRH regimen were more common in females than males, with a ratio of 5 : 1. Statistic analysis provided evidence for such a tendency ($p=0.074$).

4. *Effectiveness of TRH in relation to the length of hospital stay*

The overall effectiveness of TRH as related to the length of the present hospital stay is shown in Table 3. An excellent or good response was evoked in 9 out of 16 cases staying in hospital for less than 1 year and in 4 out of 8 cases receiving hospital treatment for 1 - 2 years, the incidence being between 50 and 56.2% for these 2 subgroups. The incidence was reduced to 25 - 40% in

patients staying in hospital for 2 - 5 years : 3 out of 8 hospitalized for 2 - 3 years ; 1 out of 4 for 3 - 4 years ; and 2 out of 5 for 4 - 5 years. Eight (38%) out of 21 patients hospitalized for more than 5 years responded either excellently or well to TRH therapy. Worthy of note here is the incidence of more or less favorable responses in the last subgroup, which was as high as 85.7% or 18 out of 21 cases.

Statistic analyses of the results disclosed no significant difference between the 2 subgroups staying in hospital for less than 1 year and for 1 year or more on the basis of the incidence of good or better responses, that of fair or better responses or that of adverse responses. No any significant difference was revealed between 2 subgroups hospitalized for less than 5 years and for 5 years or more with respect to the incidence

TABLE 3
Effectiveness of TRH in relation to the length of hospital stay

Overall effectiveness Length of hospital stay	Excellent	Good	Fair	Poor	Aggravated	Total
1 yr	6	3	3	2	2	16
1 - 2 yrs	4		1	2	1	8
2 - 3 yrs		3	1	3	1	8
3 - 4 yrs		1	1	2		4
4 - 5 yrs	1	1	3			5
5 yrs -	3	5	10	1	2	21
Total	14	13	19	10	6	62

of good or better responses or that of adverse responses, although fair or better responses tended to be more frequent in the latter subgroup ($p=0.086$).

5. *Time interval between administration and the manifestation of effect and its duration*

The time interval between the administration and the manifestation of the effect of TRH in 27 cases responding excellently or well is shown in Table 4. TRH took effect within 7 days in 26 cases, some of which responded overtly to the hormone as early as the 2nd or 3rd day of treatment. In 1 case the effect of TRH was not manifested for as long as 10 days. The duration of the effect varied in different cases: In some cases, it lasted as long as the course of the TRH regimen, but in other cases it continued for 1 month or more after TRH was withdrawn. Further investigation will be needed in this respect.

6. *Adverse side-effects*

One of the 62 patients had gastrointestinal upset, such as nausea and diarrhea, together with weight loss. It is uncertain whether these manifestations were really attributable to TRH in this patient, who had had marked hypochondriacal trends. No other serious side-reactions were seen.

7. *Report of cases*

Some representative cases, including 2 responding excellently, 1 well and 1 adversely, are illustrated below.

Case 1

K.S., a 22-year-old woman

Present history: Had the onset of

TABLE 4
Time interval until manifestation of effect

The day when TRH took effect	Number of cases
1	0
2	3
3	4
4	5
5	0
6	0
7	14
8	0
9	0
10	1
Total	27

the illness for the first time. The prepsychotic personality pattern was characterized by taciturnity, shyness and introversion. She had become increasingly insomniac since early in Sept., 1973, and often stayed confined to her bed at home, saying that she was jeered at because of her funny face (bulging forehead) and so she wanted to do nothing. She was admitted to H Hospital in such a condition on Nov. 14, 1973.

On admission the patient had the aforementioned delusions of persecution and reference with disturbance of sleep and reduced spontaneity. Saying that she couldn't get her ideas in order, she answered the questions of the psychiatrist in charge not promptly but bluntly in a whispering tone with her head drooping. Treatment consisted of haloperidol, thioridazine, diazepam and chlorpromazine, each given as appropriate. Early in Dec. she had ideas of suicide temporarily, which were then removed by 5 ECTs. Toward the end of Feb., 1974 she was no more laden with abnormal experiences but remained still expressionless with so marked loss of initiative that she took care of herself

only when urged. No symptomatic alterations were produced by subsequent combined use of chlorpromazine and propericiazine; chlorpromazine and perphenazine; or thioridazine and perphenazine.

Status prior to TRH regimen:

Though free from abnormal experiences, the patient was expressionless and unresponsive, never speaking to others but answering bluntly in a low voice with downcast eyes to the questions of the doctor in charge. She could dress, wash her face and take meals by herself. She participated in occupational programs but only with reluctance and poor results.

Status following TRH regimen: The preceding medication to which TRH was added consisted of thioridazine 150 mg, perphenazine 12 mg, diazepam 15 mg and trihexyphenidyl 6 mg. The initial serum T_4 level was 4.8 $\mu\text{g}/\text{dl}$, indicating the euthyroid state of the patient. In conjunction with the above medication, TRH, 4 mg, was administered in 2 divided doses in the morning and evening for 14 days starting on July 14, 1974. On the afternoon of the 2nd day of TRH therapy the patient looked somewhat less gloomy. She was tentatively permitted to stay out the next day when she looked fairly bright, talking of her own accord about how things were going on in the hospital, as she had never done before. She greeted or spoke to her neighbors or relatives when she saw them at home, in marked contrast to her previous retiring to the corner of the room to avoid conversation. On the 5th day the psychiatrist in charge found her looking mild and bright and giving a definite reply to his questions with her face kept raised. She reported feeling pleasant and no longer dejected. On arriving at the ward she saluted the room-mates to their dismay, as she had never done

before. Her mother saw us immediately after the patient's time at home to inform us of such a condition of her daughter with surprise. The patient became disposed to participate in occupational programs and also brisk in motion, not sluggish as before. Even with TRH regimen withdrawn after 14 days, she remained in such an improved condition: she now answered definitely that she had no more abnormal experiences and was also inclined to do her own toilet, evidence of her condition being fully ready for discharge. She left the hospital on Aug. 17, 1974. Under further ambulatory care and following, the patient has remained in the afore-mentioned condition up to the present (Jan., 1975).

Case 2

R.K., a 45-year-old woman

Present history: Had the onset in 1970. Received treatment in Kurume University Hospital for 5 months.

Around May 4, 1974 the patient complained of pain in the shoulders and loins with sleeplessness. She was confined to her bed, retiring into herself and taking little of meals. Admitted to Kurume University Hospital on May 14.

On admission the patient was clinomanic, failing to get up even at meals or to come into contact with the people around her. When asked, she replied taciturnly in an almost inaudible voice. She cried for "returning home". She complained of auditory hallucinations and delusions of presecution and reference: "I hear the neighbors talking about me I hear their voices in the air". No symptomatic relief was achieved with 150-350 mg of floropipamide given for 4 weeks. The drug was then replaced with 6-12 mg haloperidol with the result that she was almost completely relieved of the hallucinations and

delusions but not to the least of other symptoms.

Status prior to TRH regimen : Almost free from abnormal experiences but presenting with clinomania, autism and mutism, the patient looked dull, always drooping her head to avert eye contact with others.

Status following TRH regimen : The preceding medication to which TRH was added consisted of haloperidol 6mg. TRH was administered in daily dose of 4 mg b. i. d. in the morning and evening for 14 days beginning on June 21, 1974.

Around the 4th day of treatment the patient exhibited a tendency to leave her bed for televising or making a light toilet while she spoke rather more than before. Standing aloof from her bed for an increasing time span of the day subsequently, she became interested in her surroundings and also began to have a conversation with other patients both frequently and smilingly. While being interviewed, she talked with her face raised, coming into eye contact and with an improved rapport with the interviewer. She was discharged on July 12 after pursuing a favorable course for 1 week following withdrawal from TRH. Now after 1 month of ambulatory care the patient's condition has remained ameliorated.

Case 3

Y.I., a 24-year-old woman

Present history : Had the onset in May, 1971 and had been under ambulatory care at W Hospital since Aug., that year. Received treatment as an inpatient from Dec. 29, 1971 until Dec. 2, 1972 because of symptomatic aggravation and as an outpatient subsequently. Treatment was discontinued in summer, 1973. Presented with prominent emotional lability toward the end of Dec., 1973 : weeping, laughing, getting angry

at trifles and occasionally going to the length of doing violence to her mother. Had marked autism with apathy, negativism and refusal of food early in Jan., 1974, while being confined to her bed almost all day long. Admitted again to W Hospital on Jan. 14, 1974 because her nutritional state deteriorated while she was left untreated for some time. No particular symptomatic improvement ensued until early in Feb., when she suddenly fell into a stuporous state. Transferred to Kurume University Hospital in the worst condition ever experienced both mentally and physically on Feb. 20. Recovered from the stuporous state by 4 ECTs ; and became able to wash her face, take meals and change clothes although there were some symptoms persisting, such as autism, blunted affect, mutism and negativism, along with occasional episodes of what appeared to be substupor. Treated during this time with haloperidol, chlorpromazine, diazepam, levomepromazine, oxypertine and l-dopa without results. Went into a substuporous state again early in June, 1974 and then recovered by 3 ECTs but with little remission of other symptoms.

Status prior to TRH regimen : Presented with such marked symptoms, including autism, mutism, apathy and loss of rapport, as to make the patient hardly responsive to the questions of the psychiatrist in charge.

Status following TRH regimen : In addition to 12 mg haloperidol and 9 mg diazepam, which constituted the preceding medication, TRH, 4 mg, was administered in 2 divided doses in the morning and evening over a 14 days period starting on June 21, 1974. On the 4th day of treatment the patient who had so far been expressionless started greeting with a smile and responding smoothly. Then she showed improved rapport with other patients, singing

song with them, and also became obedient to the psychiatrist and nurse in charge. Moreover, she took an interest in social affairs when televiewing or reading magazines. She became capable of a substantial conversation. In behavioral terms, she acted of her own will and at her own discretion and became willing to participate in recreational programs. She replied, "I have no hallucinations or delusions now", although she appeared somewhat doubtful of the statement. Such an improved state persisted even after withdrawal from TRH, with the patient now capable of staying out though with loss of insight. The effect of TRH regimen lasted about 2 months in this case.

Case 4

F.O., a 23-year-old-woman

Present history: Sought psychiatric advice with the chief complaints of "keeping still without doing anything", "no sleep at night" and "being quick to take offense" and admitted to Kurume University Hospital on Jan. 11, 1974.

The symptomatology on admission consisted of autism, monologue, inappropriate laughter and a repulsive attitude; she was also violent occasionally, getting angry at trifles. When interviewed, she was noncooperative, keeping stubbornly silent. Her behaviors and complaints evinced the presence of auditory hallucinations, delusion of persecution and delusional mood. Various neuroleptics were administered without yielding favorable results. Sedation was somehow brought about by 8 ECTs instituted every other day. With 60 mg perphenazine and 30mg chlorprothixene given from March 8 on, she became responsive to questions, reflective on her own violence and rid of aggressive or repulsive attitude while at the same

time she denied having auditory hallucinations or delusions. The only symptom remaining refractory to TRH regimen was erotomania, which sometimes drove her into abnormal acts.

Status prior to TRH regimen: Admitted her erotomania but denied having any other abnormal experience. Expressionless, markedly abulic and slow-moving.

Status following TRH regimen: In addition to the preceding medication that consisted of perphenazine 60 mg and chlorprothixene 30 mg, TRH, 4 mg, was administered in 2 divided doses in the morning and evening for 11 days starting on July 9, 1974. She then complained of depersonalization, cenesthopathy, increased appetite and disturbance of sleep, remarking on the 3rd day of treatment, "I cannot express myself well but I feel somewhat worse"; on the 7th day, "I feel that my feet are not on the ground and my head is floating"; and on the 9th day, "I am queer in the head after taking the medicine. I feel my own identity doubtful. I feel as if my head and body were kept apart. I cannot sleep at night". Since these complaints became increasingly severe, TRH was discontinued on the 11th day of treatment. The symptoms persisted until the 8th-9th day after cessation of TRH therapy and then rapidly disappeared a few days later.

DISCUSSION

In our previous communication⁵⁾ it was reported that 4mg daily of TRH given by mouth in 2 divided doses for 2 weeks in conjunction with the preceding neuroleptics gave rise to improved rapport with a brightened look and increased physical activity in 3 out of 5 schizophrenics. In these 3 cases symptomatic relief also ensued from the addi-

tion to the psychotropic drugs of l-dopa in small amounts (300 - 400 mg daily), whereas no response was evoked by the addition of l-dopa in the other 2 cases that failed to respond to TRH.

This experience led us to the assumption that the group of schizophrenics in which TRH is indicated might be roughly identical with that in which the use of l-dopa is warranted: patients with schizophrenia manifested by reduced spontaneity, abulia, apathy and social withdrawal^{2) 3) 4)}.

In the present study TRH was administered in a daily dose of 4 mg for 2 weeks as a rule. With such a dosage level and schedule, no side-effects of special note were observed. A longer course of treatment with the hormone should be considered in the future, depending on the characteristics of the subjects.

The daily dose of 4 mg employed in this study seems to have been appropriate, in view of the effect having been manifested within a week as well as the lack of severe irritation that usually accompanies the use of this hormone.

Hollister et al.¹⁾ found presenting symptoms improved in 1, unaffected in 1 and aggravated in 2 out of 4 male schizophrenics treated orally with TRH, 300 mg daily, for 2 weeks. The excessive dosage of the hormone might be accountable for such poor results.

In treating 4 schizophrenics with TRH, Wilson et al.⁷⁾ discontinued psychotropic medication for a period of 7-15 days immediately preceding the initial dose of the hormone. In our study, in contrast, TRH (4 mg daily) was added to psychotropic medication while the latter was continued. No adverse effects ascribable to the combined use of TRH and psychoactive drugs were observed. Symptomatic aggravation, which actually ensued in 6 of our cases, might have been more frequent

if psychotropic medication had been withdrawn.

It was shown that a tendency toward symptomatic aggravation associated with TRH regimen was more pronounced in the catatonic than the hebephrenic type, although there was no distinct difference between types of schizophrenia in respect to the overall effectiveness of the hormone. TRH may be more safely used in patients of the hebephrenic type.

It seems that TRH, just like l-dopa, more readily takes effect in those patients who present with loss of initiative, abulia and social withdrawal as principal symptoms while being free from hallucinations, delusions and excitement. There is also a resemblance between the symptoms or signs that responded adversely to TRH and to l-dopa.

No specific correlation was established between the effectiveness of the hormone and the sex of subjects. Noteworthy, however, is the fact that symptomatic aggravation associated with TRH regimen tended to be more frequent in females than males. The meaning of this phenomenon is obscure.

The relationship between the length of hospital stay and the effectiveness of TRH therapy was represented by a tendency for fair or better responses to be of higher incidence among patients hospitalized for 5 years or more, a finding which we find hard to accept being opposite to that obtained with l-dopa⁴⁾. If this finding is truly reproducible, however, then it follows that TRH can be used even in patients afflicted by the illness over a fairly long period of time.

TRH took effect within a week, showing it to be extremely rapid acting. The duration of its effect varied in different cases. Further investigation will be needed in this regard. Our impression was that the effect of the hor-

mone generally lasted longer in patients who responded more favourably, although it disappeared rapidly in some instances.

That the hormone has no serious side-effects is a feature which is advantageous to its clinical use. The reason why TRH is effective against loss of initiative, apathy and autism as principal symptoms of schizophrenia or the mechanism of its action on these symptoms was discussed elsewhere⁵⁾ and so is not taken up here. A double-blind controlled study is to be undertaken with a view to verifying the therapeutic results obtained with the hormone in this study, which was uncontrolled and preliminary in nature.

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