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A DOUBLE-BLIND CROSSOVER SEQUENTIAL TRIAL OF ORAL THYROTROPHIN-RELEASING HORMONE IN DEPRESSION

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Summary In a double-blind, crossover, sequential trial, oral thyrotrophin-releasing hormone (T.R.H.) (40 mg.) given daily for a week was no more effective than placebo in treating twenty-nine depressed outpatients. There was no clinical or biochemical evidence that patients continuing on oral T.R.H. (40 mg. daily) maintenance therapy after completion of the trial became hyperthyroid, even when T.R.H. was administered for 12 weeks.

Introduction

TWO double-blind clinical trials [1,2] have shown that intravenous thyrotrophin-releasing hormone (T.R.H.) is more effective than intravenous saline solution in relieving the symptoms of depression. A single case-report [3] claimed shortlived relief of depression with oral T.R.H. These promising results led us to conduct the present investigation.

Patients and Methods

Psychiatric outpatients with depressive illness which had not responded to conventional antidepressant treatment were admitted to the trial after their antidepressant treatment had been held constant for at least 4 weeks.

The age-limits for entry to the trial were 17 and 65 years, and patients with clinical evidence of hyperthyroidism or ischæmic heart-disease were excluded.

Patients were randomly allocated under double-blind conditions to treatment with one tablet of placebo or T.R.H. (40 mg.) daily in the first week of the trial and received the alternative treatment in the second week. Patients continued to take their usual antidepressant therapy in the same dosage throughout the trial.

The principal complaints present at the start of the trial were recorded and these symptoms were rated as unchanged or worse, or improved or recovered at the end of the first and second weeks. Any new symptoms appearing during the trial were noted. From this a preference for the first or second week of treatment was recorded on the basis of the psychiatrist's observations of the mental state and the patient's own choice. A sequential method of analysis was used and, since the trial was designed to show whether or not T.R.H. was more effective than placebo, it was decided to stop the trial once T.R.H. was shown to be superior to placebo, or at a point when such a result would be impossible within the closed design

TABLE I—DATA ON PATIENTS

Patient no.	Sex	Age	Depression		Treatment	
			Type	Duration in months	T.R.H. order	Preference
1	M	28	E	4	1	Placebo
2	F	64	E	168	2	None
3	F	27	E	5	2	T.R.H.
4	F	50	R	9	2	T.R.H.
5	F	56	R	204	1	None
6	F	41	R	84	1	Placebo
7	F	53	E	8	1	Placebo
8	M	17	R	6	2	=D
9	F	30	R	24	1	=D
10	M	32	R	24	2	Placebo
11	M	50	R	5	1	None
12	F	44	R	·72	1	=I
13	F	18	R	4	1	=D
14	M	55	R	3	2	Placebo
15	F	26	R	24	1	Withdrawn
16	F	59	R	24	1	Placebo
17	F	43	R	24	1	Withdrawn
18	M	30	R	9	2	Placebo
19	F	40	R	48	1	None
20	F	29	R	48	2	Placebo
21	F	59	R	24	2	T.R.H.
22	F	25	R	24	1	Placebo
23	M	47	R	120	2	T.R.H.
24	F	62	R	18	2	Placebo
25	M	50	R	12	2	Placebo
26	F	55	R	40	2	T.R.H.
27	M	41	R	252	1	None
28	M	54	R	360	2	Withdrawn
29	F	40	R	78	1	Placebo

E=Endogenous depression. R=Reactive depression. =I indicates equal improvement. =D indicates equal deterioration.

employed.

Blood-samples were taken at the start of the trial to confirm that the patients were euthyroid. Some patients continued on T.R.H. after completion of the trial fortnight, and further blood-samples were obtained from these patients.

Results

The results are summarised in tables I, II, and III and demonstrated in the sequential chart (see accompanying figure). The sequential chart shows that it would be impossible to prove that T.R.H. is more effective than placebo at a probability level of 0·05 (one-tailed test) by continuing the trial any further. New symptoms recorded during the trial are shown in table IV. In nine patients it was impossible to discern any difference between treatment weeks—in five patients there was no change at all; in three patients there was an equal deterioration, and in one patient there was equal improvement in both weeks. Two patients were withdrawn because of "side-effects" and the third did not attend for follow-up.

There were no changes in serial thyroid-function tests (serum-protein-bound iodine, 'Thyopac' 3 and 4, calculated free-thyroxine index, and serum-thyroid-stimulating-hormone by radioimmunoassay [4]) in four patients who continued on T.R.H. for 4, 8 (two patients), and 12 weeks after completion of the trial.

TABLE II—TREATMENT PREFERENCE RELATED TO ORDER OF ADMINISTRATION OF T.R.H.

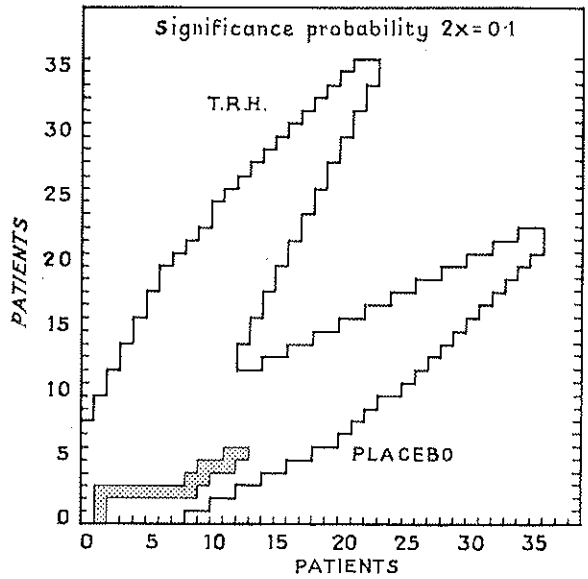
T.R.H. given	Preference			Drop out	Total
	Placebo	T.R.H.	None		
First ..	6	—	7	2	15
Second	6	5	2	1	14
Total	12	5	9	3	29

TABLE III—TYPE OF DEPRESSION RELATED TO TREATMENT PREFERENCE

Type of depression	Preference			Drop out	Total
	Placebo	T.R.H.	None		
Endogenous	2	1	1	..	4
Reactive	10	4	8	3	25
Total	12	5	9	3	29

Discussion

Our results do not accord with previous reports that T.R.H. is beneficial in depression. Kastin et al.[1] administered intravenous T.R.H. μg. or saline solution, under double-blind conditions, to five patients for 6 days, with crossover of treatment after 3 days. Two of these patients were in the depressive



Sequential Chart.

Numbers along the coordinates refer to patients who showed more improvement on T.R.H. (ordinate) or on placebo (abscissa).

phase of manic-depressive illness and three had involutional depression. The age-range was 35–64 and the group included one man. Improvement was pronounced in four patients and slight in one. The duration of improvement varied from 3 hours to 6 days.

In another double-blind study, Prange et al.[2] demonstrated that a single injection of T.R.H. (600 μg.) produced a prompt, brief improvement in unipolar depression in ten female inpatients aged between 25 and 45, while injection of saline solution did not. These patients demonstrated a striking improvement in depression an hour after T.R.H. and relapsed about 5 hours later. They had no other medication other than placebo tablets.

There is also a single case-report [3] of a 36-year-old male inpatient who demonstrated a reproducible 6-hour improvement in depression when treated with oral T.R.H. (40 mg.) but did not improve on placebo.

Our results do not accord with those of previous

TABLE IV—NEW SYMPTOMS REPORTED DURING TRIAL

Symptom	While on T.R.H.	While on placebo
Nausea	14, 15*, 27	2, 26
Abdominal pain	2, 11, 24	11
Drowsiness	5, 14, 19, 20	
Trembling	10	
Increased anxiety	11, 12	7
Skin lesions	9	22
Hesitancy in speech	10	
Headache	21, 23, 27	21, 28
Back pain	26, 27	26
Dizziness	17*	21
Increased smoking	22	

Numbers refer to the trial number.
* Indicates symptom which caused the patient to withdraw from the trial.

trials, possibly because of the T.R.H. dosage chosen; the population studied; observer bias; the choice of trial design; and the fact that we used oral T.R.H.

Ormston et al.[5] demonstrated that oral T.R.H. at a dosage of 20 mg. and above produced a consistent rise in serum-thyroid-stimulating-hormone (T.S.H.) and reached a mode peak response 2 hours after ingestion of the tablet. Poor absorption is therefore unlikely to have affected our results. The dosage chosen was higher than that used by van der Vis-Melsen et al.[3] in their successful maintenance treatment (10 mg. daily). A higher dosage might have been used, but it is known that two doses of 80 mg. T.R.H. daily can cause an important increase in circulating thyroid-hormone levels and that five doses of 80 mg. produce clinical hyperthyroidism in normal volunteers. These findings suggest that our dosage was appropriate in our present state of knowledge.

Psychiatric patients are unreliable in taking their medication,[6,7] but our patients were seen weekly and residual pills were counted at each visit. Apart from the patients who dropped out of the trial, only two patients had residual tablets at the end of one of the trial weeks. Patient 9 omitted one of her T.R.H. tablets because she felt they were making her worse and patient 13 omitted two of her tablets because of a suicide attempt. It was impossible to discern any difference between treatment weeks in either of these patients, so they do not contribute either positively or negatively to our results.

Our patients differed from those in the other studies because they had mainly reactive rather than endogenous depression, they were outpatients, and had been unresponsive to conventional antidepressant drug therapy. They therefore represent a formidable challenge to any new antidepressant treatment, but a reasonable one in view of the dramatic results so far reported.

Ormston's report [8] on the response of normal subjects to 40 mg. oral T.R.H. showed that T.S.H. levels returned to a basal level within 12 hours. None of the patients participating in our trial reported any regular elevation of mood in the few hours after drug ingestion. Although the treatment order in our trial was randomly and blindly allocated, table II shows that the only patients to respond to T.R.H. did so when it was the second treatment, and that there was an excess of patients in whom it was impossible to show any difference between treatment weeks when T.R.H. was given first. Since Kastin reported [1] that the antidepressant effect of T.R.H. lasted up to 6 days in one patient, we considered the possibility that the failure to discriminate between weeks was due to a carry-over of benefit from the first week's treatment. A carry-over effect is unlikely since four patients (5, 11, 19, 27) showed no improvement at all, two patients (9, 13) showed equal deterioration in both weeks, and in only one patient (12) was there equal improvement.

The previous studies used various ways to measure change in mood. Although our method of recording the patient's and psychiatrist's preference for one week over the other may appear crude, it closely accords with clinical practice and has been shown [9,10] to be a valid and reliable method of discriminating between treatments. A sequential trial is an economical and valid method of testing a drug.[11]

Observer bias is unlikely to have contributed to our negative results, because the psychiatrists expected that T.R.H. would be an effective antidepressant and the treatment was introduced to the patient with enthusiasm. Also, of the patients not recorded on the chart (see fig.), five were unchanged, three were worse, and only one was better. Some patients continued on T.R.H. after completion of the trial. Of the patients starting on maintenance treatment only one remained well enough to complete 3 months of therapy, and the remainder had their treatment stopped because they felt it was not benefiting them.

This also indicates the lack of efficacy of T.R.H.

Transient side-effects have been observed after rapid intravenous injection of T.R.H., but the consensus of opinion [12] is that oral T.R.H. does not usually produce important side-effects. There have been occasional reports of slight nausea. The only two patients who withdrew from the trial because of side-effects did so while receiving T.R.H. Patient 15 complained of nausea, vomiting, and general exacerbation of her psychiatric symptoms, while patient 17 felt faint and dizzy before " collapsing " about an hour after taking her first tablet. New symptoms appearing during the trial are shown in table IV. Seventeen patients complained of new symptoms during the week they received T.R.H., and only seven complained in the placebo week ($\chi^2=7{\cdot}1$, $P<0{\cdot}01$).

While no therapeutic effect has been demonstrated in this trial, information has been obtained on the effect of prolonged daily administration of 40 mg. oral T.R.H. There was no biochemical evidence of hyperthyroid changes, even when 40 mg. T.R.H. was administered for 12 weeks.

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