RESEARCH PAPER

Thyroid Functioning During Treatment for Depression

Maria Kusalic, M.D.[1], Frank Engelsmann, Ph.D.[2], Jacques Bradwejn, M.D.[1]

[1]Department of Psychiatry, McGill University, Montreal, Quebec, [2]Department of Psychiatry, Allan Memorial Institute, Royal Victoria Hospital, Montreal, Quebec

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Thirty-nine unipolar depressed patients were treated, after a washout period of seven days in a double blind study with either moclobemide, placebo or amitriptyline, for 42 days. The psychopathological assessment and HRSD were done on seven day intervals and thyroid analysis was done on 14 day intervals. At the end of therapy, the levels of T4 and fT4 decreased significantly in the responders if amitriptyline was used, and non-significantly if placebo or moclobemide were used. The T4 and fT4 values of the non-responders increased non-significantly. The weight change was minimal and non-significant.

Key Words: depression, thyroid hormones, antidepressants, tricyclics, monoamine oxidase inhibitors, moclobemide

INTRODUCTION

The role of thyroid physiology in depression or during its treatment is still controversial. Linnoila et al (1981) reported that thyroid functioning was unchanged during treatment of major depression with tricyclic antidepressants (TCAs). Others have reported that initial higher normal values of T4 and fT4 decrease in parallel to recovery from major depression in hospitalized patients treated with various tricyclics (Brady and Anton 1989; Joffe and Singer 1990; Muller and Boning 1988; Roca et al 1990). Several researchers have also reported changes in TSH values during recovery from depression after treatment with tricyclics (Brady and Anton 1989; Muller and Boning 1988; Roca et al 1990). Only one study reported no change in thyroid functioning during treatment for major depression with phenelzine (Joffe and Singer 1987).

Although evidence suggests that recovery from depression is reflected by changes in thyroid functioning, it is still unclear whether changes in thyroid functioning are related to pharmacotherapy or to the natural course of illness, given that none of the above studies incorporated a placebo group in their design.

The objective of this study was to assess changes in thyroid functioning among depressed patients. Serial assessment of thyroid functions were performed before, during and after treatment.

METHOD

Subjects

The subjects entered the study, on an outpatient basis, if they suffered from a major depressive episode according to the DSM-III-R criteria and had a score of 18 or more on the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton 1967). The subjects were in good physical health, according to a physical examination, a complete blood count, a chemistry profile including thyroid functions and an electrocardiogram. All subjects gave their written informed

Address reprint requests to: Maria Kusalic, M.D., St. Mary's Hospital, 3830 Lacombe, Montreal, Quebec, Canada H3T 1M5.

Table 1

Treatment response and thyroid changes in all three groups of patients

	HRSD Scores		T4		fT4I		TSH	
	I (n = 23)	NI (n = 16)	I (n = 23)	NI (n = 16)	I (n= 23)	NI (n = 16)	I (n = 23)	NI (n = 16)
Day 0	24.3	23.8	98.4	106.0	27.6	29.1	1.6	1.1
Day 42	5.2[a]	19.5	91.7[b]	108.3	25.9[b]	30.8	1.5	1.0

I = improved; NI = not improved; [a]significant at p = 0.000; [b]significant at p < 0.05

consent to participate in the study. Fourteen females and 25 males participated. The patients whose scores on the HRSD improved more than 20% or whose scores were lower than 18 after the lead-in period were excluded from the study.

Design

The study was double-blind with three parallel treatment groups: one receiving amtriptyline, one receiving moclobemide and one receiving a placebo. All were preceded by a placebo lead-in period of one week.

Treatment

The patients received treatment with one of the following medications over a 42-day period: amitriptyline (mean dose = 109.93 ± 5.11), moclobemide (mean dose = 482.60 ± 5.53), or placebo. The medication was given in capsules that were identical in shape, size and color.

Measurement

The patients were assessed every seven days for psychopathology using the HRSD. Blood samples were drawn every 14 days for thyroid assays.

Thyroid assays

All thyroid function tests were performed by coated-tube RIA methodology. T4 and T3U (ImmunoCorp, Montreal, PQ) assays had mean control inter-assay CVs of eight percent for T4 and four percent for T3U. TSH (BioRad CoTube TSH IRMA, Mississauga, ON) was assayed using a high-sensitivity TSH method (sensitivity = 0.05 mU/L) with a mean control inter-assay CV of six percent. Total T3 (Kallestadt Quanticoat T3, Sanofi Diagnostics Pasteur, Montreal, SPQ) had mean control CVs of seven percent.

Statistical analyses

A multivariate analysis of variance (MANOVA) was used to determine the effects of the medication on hormonal variables over time (T) in the three groups (G), and the interaction of G × T. T-tests were used to examine whether there were significant differences in sex, age, HRSD scores and all hormonal variables between those who had improved with treatment (I) (n = 23) and those who had not improved with treatment (NI) (n = 16). Improvement was defined as a 50% decline in the HRSD score by the end of the treatment period.

RESULTS

Subjects' characteristics

Twenty-five males and 14 females were included in the study (N = 39), with a mean age of 41.3 ± 10.1, ranging from 22 to 61 years. There were no age differences between the males and females in the sample as a whole; the average age was almost identical, near 41 years. There were no differences in age between the two sexes in the three groups, nor between the NI and I males and females in the three medication groups. The average age of the NI patients was 43 years and of the I patients, 40.8 years. The NI patients were older, but the age difference was not statistically significant.

The placebo group of NI patients was the oldest, with a mean age of 49.2 years, and the amitriptyline NI patients were the youngest, with a mean age of 32.3 years. The placebo I group was the youngest, with a mean age of 44 years. However, the age differences were not statistically significant.

Pearson product-moment correlations of age with the final variables (at day 42) were not significant in the placebo group (n = 15) except on the HRSD scores (r = 0.57, p < 0.03). The older patients had higher final HRSD scores. In the TCA group (n = 13), the age correlated only with the TSH at day 42 (r = 0.54, p < 0.056); the higher the subject's age, the higher the TSH value. None of the final scores correlated significantly with age in the moclobemide group (n = 11).

Response to treatment

In total, 23 patients (60%) had improved by the end of the 42 days of treatment. Table 1 shows that only six (40%) of the 15 patients treated with placebo improved, compared with ten (77%) of the 13 patients treated with amitriptyline and seven (64%) of the 11 patients treated with moclobemide. The findings must be interpreted with caution, since the small number of responders (n = 3) in the amitriptyline group limit the extent to which the results can be generalized. The small sample diminished the possibility of rejecting the null

Table 2

Thyroid hormones and medication

	Placebo		TCA		MAOI	
	I (n = 6)	NI (n = 3)	I (n = 10)	NI (n = 3)	I (n = 7)	NI (n = 4)
$T_{4\text{-}0}$	105.7	108.7	97.1	103.7	94.5	101.3
$T_{4\text{-}42}$	101.5[a]	114.1	85.7[a]	90.3	91.8[a]	108.5
$fT_{4\text{-}0}$	30.0	30.1	26.7	26.7	27.1	27.5
$fT_{4\text{-}42}$	29.5[a]	32.8	23.5[a]	23.7	26.1[a]	31.8

[a]significant at $p < 0.5$; I = improved; NI = not improved

hypothesis and finding a significant difference, if it was present (Type II error).

Changes in thyroid indices during treatment

The improvement in HRSD scores is associated with a decrease in T4 and in fT4I levels in the I group, reaching significance at $p < 0.005$ (Table 1). These changes were absent in the NI group. Table 1 shows the HRSD scores and the T4 and fT4I values for all patients receiving treatment. The thyroid changes were analyzed for individual treatment groups (Table 2): only the I group treated with amitriptyline showed a decrease in T4 ($p < 0.01$) and fT4 ($p < 0.001$) levels. T-tests on the entire sample (N = 39) showed no difference between the groups that did not lose weight (n = 31) and those who lost weight (n = 7) before treatment in the I group ($p < 0.064$).

DISCUSSION

The findings show that a major depressive episode was associated at baseline (day 0) with a relative elevation in T4 and fT4I levels. This relative elevation normalized in the I group, paralleling clinical and HRSD evaluations. In contrast, decreases in thyroid functioning were not seen in the NI group. This normalization seemed to be a reflection of decreases in T4 and fT4I levels in the amitriptyline-treated patients only ($p < 0.01$ and $p < 0.001$, respectively). The lack of a significant decrease in the placebo and moclobemide groups may be a function of the smaller number of subjects studied. However, decreases in thyroid indices during recovery from depression may be related specifically to treatment with a TCA and not to a monoamine oxidase inhibitor.

Table 3

Weight and thyroid hormones among the patients who had improved

	No weight change (n = 16)	Weight loss[a] (n = 7)
$T_{4\text{-}0}$	103.9 ± 15.5	93.4 ± 31.2
$T_{4\text{-}42}$	97.0 ± 17.7	81.1[b] ± 18.8
$fT_{4\text{-}0}$	28.9 ± 4.9	26.6 ± 7.9
$fT_{4\text{-}42}$	26.6 ± 5.7	24.6[b] ± 6.9

[a]weight loss more than two pounds from baseline weight; [b]$p < 0.064$, reaching significance

The findings of this study are supported by reports of decreases in thyroid indices following clinical recovery from depression after treatment with TCAs, ECT, lithium and carbamazepine (Cohen and Swigar 1979; Kirkegaard and Faber 1981; Kolakowska and Swigar 1977; Morley and Shafer 1982; Amdisen and Anderson 1982; Roy-Byrne et al 1984).

These findings are also supported by data from a study by Joffe and Swigar (1987), who found that improvement in depressive symptoms after treatment with phenelzine was not associated with a significant alteration of thyroid functioning. Further comparative studies are warranted to determine whether or not TCAs have specificity effects on thyroid changes during recovery from depression.

The mechanism by which amitriptyline results in this decrease in thyroid functioning is not known. Rubin (1987) suggested that weight loss during depression may result in increases in T4 values. Azizi (1978) reported that changes in T4 associated with prior weight losses were greater in men. Eight of the subjects in this study reported having lost weight. Of these eight subjects, seven responded to treatment, five of whom were males; however, only one of these subjects had been treated with amitriptyline.

Brady and Anton (1989) suggested that the decrease in thyroid indices seen after treatment with desipramine may be related to a down-regulation of the thyroid axis at the level of the hypothalamus. In contrast, Ferustrom et al (1985) suggested that this decrease may not be specific, but may result from a decrease in resting metabolic rates induced by a tricyclic antidepressant. The changes in thyroid status observed after treatment with amitriptyline may be a reflection of sedation or of the action of this drug on the serotonin system. Thus, differences in changes in thyroid values between amitriptyline- and phenelzine-treated patients may

reflect differences in their effect on the serotonin system (de Montigny 1991).

The observed changes after treatment with amitriptyline may be specific to tricyclic antidepressants but unrelated to the effects on the serotonergic system. Shelton et al (1993) reported that desipramine, but not fluoxetine, was associated with an increase in total T4 during treatment for depression. The mechanism by which antidepressants decreased T4 and fT4 levels during treatment is still unknown and deserves further research.

More work is necessary to understand the mechanism by which TCAs result in a decrease in thyroid functioning during recovery from depression and whether or not this decrease is related to the neurobiology of depression.

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