A DOUBLE BLIND CROSSOVER TRIAL ON LEXOTAN AND PLACEBO IN THE TREATMENT OF PATIENTS WITH PSYCHOPHYSIOLOGICAL DISORDERS

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Many psychopharmacological agents are now available for the treatment of psychiatric patients from the somatotherapeutic point of view as part of the comprehensive approach. The tranquillizers, also called "minor tranquillizers", are widely used in the handling of the 30% – 50% psychoneurotic and psychosomatic patients in the daily medical practice (1) as an important complement to other therapeutic means.

Lexotan or Bromazepam (Ro 05–3350 of Hoffmann-La Roche laboratories), a benzodiazepine derivative, has entered the arena and careful studies are being conducted now as in phase III of clinical research aspects of psychotropics (4) to establish the effectiveness of this new-comer. The "true drug effect" can only be determined by comparing it with a placebo, as was done in this study.

Material and Method

All patients with predominant psychophysiological complaints, without organic disorders, and who are willing and able to participate, are included in this controlled double blind crossover clinical trial. Pregnant women were excluded. So were patients of 50 years and over for eventually organic changes in the brain.

The drugs, all in the form of 3 mg.tablets, with a placebo as reference, were administered to the patients on an ambulatory basis at random according to the table of randomization of Moses and Oakfor (3). In the first week two times, one tablet a day was given, and further three times, one tablet a day until the end of the six-week trial. If the patient was taking other psychotropic drugs already, they were stopped for 2 – 3 days to allow a "wash-out" period (2). A crossover was done after four weeks.

Assessment of specific symptoms (7 categories of 15 psychic and 39 somatic symptoms) was done according to a 4-point rating scale (0 = absent, 1 = slight, 2 = moderate, and 3 = marked) before trial and further at a biweekly interval until the end of the sixth week. Routine laboratory tests for blood (white and red blood cells, haemoglobin, sugar-fasting, urea) and urine.(protein, sugar, bilirubin, urobilin, sedimentation) were also done before trial and during the last week.

At the end of the fourth week (before crossover) and of the sixth week (after crossover) a general assessment was made by the investigator and patient according to a 5-point rating scale (very good, good, moderately good, producing no change and causing deterioration) as was also done for the general tolerance (rated: good, moderate or unsatisfactory). Occurring side effects were stated as transient or lasting. Adjunctive therapy was given only when it was really necessary.

RESULTS

50 patients were evaluated and after the key was known, it appeared that 24 patients (5 men and 19 women between 17 and 48 years with a mean age of 32.0) started with Lexotan and 26 (12 men and 14 women between 17 and 39 years with a mean age of 27.5) with placebo.

46 patients had previous therapy already, 39 with various psychotropic drugs, most of them combined with other drugs as analgesics and spasmolytics, a few also had massage. Of these patients, only 11 had moderately good results with the previous therapy, the others reported no improvement.

The duration of the disorders in the Lexotan group is between 1 month and 10 years with an average of 129 weeks. In the placebo group it is between 3 weeks and 8 years with an average of 68 weeks.

Of the 26 placebo patients, there were 5 drop-outs: 3 before and 2 after crossover. After home visits and inquiries, it was found out that of those 3 one went back to his village without further message, 2 stayed away because they felt no improvement. Of the other 2 who did not return after crossover for final evaluation, one felt better already and went out of town for business. The other one, a female student, attempted suicide 3 days after crossover from placebo to Leoxtan with 22 tablets (= 66 mg) Lexotan because of

growing depression which was masked by her many somatic complaints. She was seen 2 days after her suicide attempt and was admitted to the hospital in the Department of Internal Medicine. She stated that she was not unconscious but had only a tired feeling and a heavy head during the first day.

Of the 24 Lexotan patients, one dropped out before crossover, a young man with a queer personality, who was not to be found at his given address. One did not come back after crossover because he went to help his father in the village who had difficulties with his business. The patient, a senior high school student with ideals for intellectual performance, had to stop his study, which was one of his major conflicts, but in spite of this until crossover he was not deteriorating and took the decision.

Adjunctive therapy was given to one patient with Lexotan before crossover (Mogadon when necessary) and to 4 after crossover to placebo. This was also done to 5 placebo patients before crossover and to none after crossover to Lexotan.

Table I and II show that the physician's rating for Lexotan patients before crossover is 43.5% very good and good to 26.1% for placebo patients. ($P > 0.05$). The patients' rating for Lexotan is 47.8% very good and good to 34.8% for placebo ($P > 0.10$).

The physician's rating after crossover from Lexotan to placebo is 27.2% very good and good and from placebo to Lexotan 57.1% ($0.01 < P < 0.05$). The patients' rating for very good and good after crossover from Lexotan to placebo is 27.2% and from placebo to Lexotan 47.6% ($0.01 < P < 0.05$).

The mean morbidity score of the group starting with Lexotan is 30.0 before trial, 12.9 before crossover (percentage fall in mean = 57.0) and 20.4 after crossover (there was a deterioration and the percentage rise in mean = 57.7) as can be

Table I

	4 weeks Lexotan (before crossover)		2 weeks placebo (after crossover)	
	Physician	Patient	Physician	Patient
Very good	6 (26.1%)	5 (21.7%)	3 (13.6%)	3 (13.6%)
Good	4 (17.4%)	6 (26.1%)	3 (13.6%)	3 (13.6%)
Moderately good	7 (30.4%)	7 (30.4%)	2 (9.1%)	2 (9.1%)
Producing no change	5 (21.7%)	4 (17.4%)	2 (9.1%)	1 (4.6%)
Deterioration	1 (4.4%)	1(4.4%)	12 (54.6%)	13 (59.1%)

Physician's and patients' general assessment of treatment of group starting with Lexotan and crossover to placebo.

Table II

	4 weeks placebo (before crossover)		2 weeks Lexotan (after crossover)	
	Physician	Patient	Physician	Patient
Very good	1 (4.4%)	1 (4.4%)	5 (23.8%)	5 (23.8%)
Good	5 (21.7%)	7 (30.4%)	7 (33.3%)	5 (23.8%)
Moderately good	6 (26.1%)	7 (30.4%)	4 (19.1%)	6 (28.6%)
Producing no change	10 (43.4%)	7 (30.4%)	2 (9.5%)	3 (14.3%)
Deterioration	1 (4.4%)	1 (4.4%)	3 (14.3%)	2 (9.5%)

Physician's and patients' general assessment of treatment of group starting with placebo and crossover to Lexotan.

Table III

4 weeks (before crossover)		2 weeks (after crossover)	
Lexotan	– 57.0	Placebo	+ 57.7
Placebo	– 40.5	Lexotan	– 42.7

Decrease or rise in mean morbidity score expressed as the percentage fall (–) or rise (+) in mean of the Lexotan and placebo groups before and after crossover.

Table IV

	4 weeks (before crossover)			2 weeks (after crossover)	
	Psychic Symptoms	Somatic Symptoms		Psychic Symptoms	Somatic Symptoms
Lexotan	–46.7	–61.8	Placebo	– 1.8	+ 97.4
Placebo	–45.3	–37.8	Lexotan	–28.1	–50.8

Decrease or rise in mean of the psychic and somatic morbidity scores expressed as the percentage fall (–) or rise (+) in mean of the Lexotan and placebo groups before and after crossover.

seen in table III. Of the group starting with placebo, the mean morbidity score is 30.9 before trial and 18.4 before crossover (percentage fall in mean = 40.5) and 10.5 after crossover (there was further improvement and the percentage fall in mean = 42.7).

If the symptoms are broken down in psychic and somatic ones, the results can be seen in table IV: the somatic symptoms showing the best results for Lexotan with a percentage fall in mean of 61.8 before crossover to placebo and 50.8 after crossover from placebo against 46.7 and 28.1 for psychic symptoms. After crossover to placebo, the mean score of somatic symptoms deteriorated with 97.4%, that of the psychic symptoms improved further with 1.8%.

Of the Lexotan group the mean blood pressure in mm. Hg. in lying position before trial, before crossover and at the end of the trial is: systolic = 125, 114 and 121, and diastolic = 80, 73 and 76; in standing position it is: systolic = 132, 117 and 122, and diastolic = 83, 77 and 80. Of the placebo group it is: systolic = 119, 116 and 115 lying, and 129, 123 and 122 standing; diastolic = 75, 74,and 71 lying, and 82, 79 and 77 standing.

Of the Lexotan group the average pulse rate per minute is: 86 before trial, 82 before crossover and 79 after crossover; for the placebo group it is: 87, 82 and 80.

Concomittant effects registered in Lexotan patients were slight drowsiness, in 3, of whom 2 were transient and 1 lasting. Slight tiredness was reported by one and a transient dry mouth by another. Two placebo patients complained also of drowsiness during the first two weeks No side effects were found in the laboratory tests done.

DISCUSSION

Although the number of patients is very limited, we can see that Lexotan scores significantly higher than placebo for very good and good (Lexotan effect 43.3% against placebo effect 26.1%), although the average duration of the disorders in the Lexotan group is much longer than that in the placebo group (129 weeks against 68 weeks). The low placebo effect may be explained by the rather high number of "old" patients (in the Lexotan group 8 new patients and 16 old patients with a total visit of 144 times; in the placebo group 10 new and 16 old patients with a total visit of 93 times) and also that minimal superficial expressive psychotherapy was done.

Before crossover, the percentage fall in mean morbidity score of the Lexotan group is also much higher than that of the placebo group. After crossover from placebo to Lexotan, further improvement was found, while after crossover from Lexotan to placebo there was a significant deterioration.

There was a decrease in the mean blood pressure (but still within normal limits for our patients) of the Lexotan group before crossover and a slight increase after crossover to placebo. Of the placebo

group there was a slight decrease before crossover and until the end of the trial. The mean pulse rate in both groups decreased slightly before and until after crossover. This decrease and increase may be explained as the patients became less or more tense in the course of the trial.

The dose used in this trial is very low: 9 mg Lexotan a day. Tjandra and Kusumanto Setyonegoro (5) in an open trial on Lexotan gave 18 mg – 20 mg a day to most of their patients, followed by a group with 24 mg. – 30 mg. a day and their result was 50.8% very good and good.

SUMMARY

A double blind crossover trial on Lexotan or Bromazepam (Ro 05–3350 of Hoffmann-La Roche Laboratories) versus placebo was done in the treatment of patients with predominant psychophysiological symptoms on an ambulatory basis.

The average duration of the disorders happened to be considerably longer in the Lexotan group (129 weeks) than in the group starting with placebo (68 weeks).

Lexotan did much better than placebo with a decrease in the average morbidity score expressed as the percentage fall in mean of 57.0 for Lexotan before crossover to placebo and a rise (deterioration) of 58.1 after crossover to placebo, against a fall of 40.5 for placebo before crossover and a further fall (improvement) of 42.9 after crossover to Lexotan.

Lexotan scores better for the somatic than for the psychic symptoms as the percentage fall in mean morbidity scores show 61.8 against 46.7 before crossover (4-week treatment) and 50.8 against 28.1 after crossover (2-week treatment).

Minimal undesirable concomittant effects were found.

Lexotan or Bromazepam, a new benzodiazepine derivative, may be of valuable help in the treatment of patients with psychophysiological disorders.

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THE MANAGEMENT OF GILLES DE LA TOURETTE'S SYNDROME BY CHEMOTHERAPY

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INTRODUCTION

The syndrome of multiple tics accompanied by explosive utterances was originally described by Itard in 1825 and was later differentiated into a syndrome by Gilles de la Tourette (1885) when he described eight cases. The following features are considered essential for the diagnosis of Gilles de la Tourette's syndrome, namely:

1. Childhood onset (below the age of 16)
2. Multiple motor tics
3. Unprovoked loud utterances, which may progress to the forced shouting of obscenities (coprolalia).

According to Fernando (1967), the illness usually commenced with multiple motor tics sometimes accompanied by utterances (vocal tics).