An Alternative Treatment Strategy With Calcium Channel Blockers in Tourette's Disorder *

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ÖZET

Bu çalışmanın amacı Tourette bozukluğu (TB)'nda kalsiyum kanal blokerleri ile alternatif bir tedavi stratejisinin izlenmesi ve bunun değerlendirilmesidir.

Bu açık çalışmada, DSM-III-R ölçütlerine göre TB tanısı konmuş 15 yatan erkek hasta, tesadüfi örnekleme yolu ile verapamil (n=8) ve nifedipine (n=7) şeklinde iki gruba ayrılmışlardır. 14 haftalık bir sürede verapamil 120 mg/gün ve nifedipine 30 mg/gün verilmiştir. 14 hafta sonunda bütün hastalarda klinik olarak belirgin düzelme meydana gelmiş, ayrıca her iki ilacın yan etkileri de tolere edilebilmiştir.

Anahtar kelimeler: Tourette bozukluğu, kalsiyum kanal blokerleri, nifedipin, verapamil

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SUMMARY

The purpose of this study was to evaluate on alternative treatment strategy with calcium channel blockers in Tourette's disorder (TD).

In an open-trial of 15 male inpatients diagnosed as TD according to DSM-III-R critaria patients were divided into two groups randomly (verapamil) (n=8) and nifedipine (n=7). Verapamil 120 mg per day and nifedipine 30 mg per day were given over a period of 14 weeks. After 14 weeks clinically obvious improvement had occured in all subjects, furthermore both drugs caused tolerable sideeffects in the patients.

Key words: Tourette's, disorder, calcium channel blocker, nifedipine, verapamil

INTRODUCTION

First described by Gilles de la Tourette in 1885, Disorder (TD) [14] is sometimes named "*tic convulsif*". Generally it starts between the ages of 2-12. Apart from grimacing, there are stereotypic tics. At the onset of the disease, those tic-like movements are seen on the upper half of the body. Later on, they spread to the whole body. Jumping, joggling, springing, talking with spitting-like noises, coughing, swearing, tooth-grinding, echolalia, sometimes coprolalia can be seen.

The tics can be voluntarily suppresed for as a number of hours. In males it is seen three times more frequently than females. Many authors have suggested psychological etiology, while some workers have expressed some organic disorders underneath [12,13, 14]. In organicity studies made in patients; EEG abnormalitles, minimal Brain Dysfunction, learning

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difficulties, concentration difficulties, pathological findings in CT scans, mild to mode rate organic disordes in organicity tests are found. All of these point to a organic basis for TD [12,13,14]. In the treatment of this disorder haloperiod is used traditionally. In doses a low as 2-10 mg haloperidol for 1-4 years have favourable outcome in 80 % of the patients [7,12,14] it has been suggested that there is a dopaminergic hyperactivity in TD, and that haloperidol has a number of side effects; namelly akinessia, depression, blurry vision, cathissia, and dyskinesia and also the fact that no response to treatment can be obtained in some patients have led to alternative treatmens [3-5-7-13-17-19]. Fluphenazine and perphenazin used in place of haloperidol are not as effective, it has been reported [7,8,12,14].

Of the alternative therapies, the one the first springs to mind is the use of calcium-channel blockers (Nifedipine, nimodipine, verapamil, diltiazem, pimozide, thioridazine) [5,7,8,12,13,15,19].

Ca^{++} is a fundamental message transmitter. It is thought that Ca has important effects on central nevvous system and emotions as well as its peripheral effecets.

Ca^{++} channels. When the action potential has spread and the relevant neurotransmitter or hormone is connected to the receptor, the calcium channels are opened. When calmodulin and Ca ions are combined, adenly cyclase is stimulated. Adenly cyclase inducts enzymatically the c-AMP formation. The secondary messanger c-AMP activates norepinephrine and throsine hydroxilase enzyime (TH).

TH is effective in NE synthesis. Ca^{++} ions are also effective in neurotransmitter discharge in brain synaptosmes with different mechanisms, and in receptor binding. In some studies it has been seen that in mania, intracellular Ca^{++} concantrations increase. There is a great relation between affection, Ca^{++} in erytrocyte and ATP activity. As a matter of fact ß-blockers and phenothiazines which bind calmodulin (which is effective on intracellular Ca^{++} concentration) and calcitonin, which decreases free Ca^{++} ions, are effective on the agitations in mania. In depression, Li lowers the Ca^{++} concentrations and thus has a antidepressant effect [1].

First generation calcium channel blockers (CCB) like nifedipine and diltiazem have been introduced in the 1970's after Verapamil. They were used as antihypertensive and coronary dilatator. Afterwards second-generation CCB like nicardipine, ambdipine maleate, felopidine, isradipine, nimodipine, nisoldipine and nitredipine were introduced and the first-generation CCB's tended to be forgotten as antihypertensives. Yet recently Verapamil has started to become important again, this time as an alternative to neuroleptics and CCB's as drugs for the treatment of mania, schizophrenia, major depression, TD, tardive dyskinesia, phencyclidine intoxication and other psychiatric disorders as alternatives to antipsychotics [2-12,3-5,7-13,15-17,14,17].

Pickar et al (1987) gave verapamil to 7 chronic schzophrenics for 5 weeks and made a double-blind placebo-controlled study. It was found that verapamil reduces blood and plasma MHPG levels [16].

Walsh et al (1986) gave 60 mg/day verapamil to a patient with TD. Vocal and motor tics improved, irritability and compulsive symptoms decreased. After a therapy of 6 months, the drug was withdrawn and the symptoms relapsed. Subsequent return to the drug regime stopped the relapse of symptoms [18].

In a previous study in Psychiatry Clinic of Gülhane Military Medical Academy (GATA) and following in 1991, Psychiatry Service of GATA Haydarpaşa Training Hospital we gave 60 mg/day verapamil to two and 2 mg/day primozide to two of 4 male patients with TD for 8 weeks. These patients, having haloperidol intolerance, improved with a decrease in hyperactivity, anxiety and irritability; with an increase in the ability to hold oneself from responding to external impulses. This improvement starded in the verapamil group after the second week and in the pimozide group after the tenth day. After the third week improvement in echopraxia and echokinesia and decrease in echolalia and coprolalia occured [4,6].

We started the present study with the hypothesis that CCB's are beneficial in TD and tried to find the role of organicity in the etiology.

MATERIALS and METHOD

Our study group was comprised of 15 male in patients with mean age of 21 and an age range of 20-22 with a diagnosis of TD. 15 males from the Psychiatry Clinic of GATA Haydarpaşa Training Hospital privates matched according to age, educational status and socio-economic stadus with the study group were selected as the control grup. The mean age of the control group was 21.1±0.4 (range 20-22). In both groups, MMPI, Bender Visiomotor Gestalt test (BVMGT), Benton Visual Memory Test (BVMT) were applied; and neurological soft signs (NSS) and minor physical anomalies were looked for. All patients had their craniographies, computerized tomography scans, ECG's and EEG's taken.

Also the routine blood and urine samples were examined and VDRL test was made. Also the hormone levels in the patients were assesed with RIA. The arterial blood pressures and body temperatures were taken regularly every day. After all these were made, those patients that have not used any psychotrophic drug were devided to two groups. The first group, comprising of patients, were given verapamil 40 mg t.i.d. (120 mg per day); while the second group comprising of 7 patients, were nifedipine 10 mg t.i.d. (30 g per day). Both drugs were given over a period of 14 weeks.

Patients from both groups were controlled two times every week (Monday and Friday) by psychiatry specialists as to assess how long the symptoms could be suppressed. The results were compared using students" "t" test.

RESULTS

Patients whose symptoms or history is specially interesting are seen in table I. The routine blood, urine tests, pulse, arterial bloodpressure, ECG and hormone levels were normal and VDRL results were negative in all patient. The MMPI, BMVGT and BVMT results are in table I and II; EEG results are in table III. The two-sided craniography and CT scans were normal.

In 12 patients (80 %) there was a psychological or physical trauma before the onset of the disease. Their social adaptibility and work was poor and their problems increased during the military service, due to the fact that they had to live together with others.

In BVMGT, 9 patients (60 %) patients had a positive (+) organicity, while 3 patients had a doubtful (±) organicity. This result was slighthly higher than the control group, but not statistically significant. In BVMT, widespread defect in 8 patients (53 %) and doubtful organicity in 5 patients (50 %) was found.

Table 1. Distribution of MMPI and organicity tests (BVMGT, BVMT, NSS, MPA) results in research group

Case	Middly increased MMPI scales	BVMGT	BVMGT	NSS	MPA
I	Paranoia	+	+	+	-
II	Depression	+	+	+	-
III	Paronoia and psychastheia	-	-	-	-
IV	Mania and hypchondriasis	+	+	+	-
V	Psychopaty	+	+	+	-
VI	Psychastheia	+	+	+	Electric hair
VII	Schiozidy	-	-	-	-
VIII	Mania, psychopathy	+	+	+	-
IX	Psychasthenia	+	-	+	-
X	Psychasthenia	-	-	-	-
XI	Psychastenia, hypochondriasis	+	+	+	*"O"*
XII	Depression	-	-	+	-
XIII	Paranoia	-	-	-	-
XIV	Schiozidy	+	+	-	-
XV	Schiozidy, hypochondriasis	+	+	+	-

Table 2. Comparison of mean values (X) standart deviation (SD) and "t" volumes of research and control groups

MMPI scale	Research group (n=10)		Control group (n=10)		t
	X	SD	X	SD	
L	5.610	2.784	5.416	2189	0.172
F	12.973	8.882	11.699	8196	0.229
K	10.966	5.061	12.269	4462	0.314
Hs	14.984	3.807	12.619	12176	0.969
D	19.644	5.081	21.214	4560	0.761
Hy	20.861	4.997	20318	4581	0.817
Pd	29.814	5.480	22.033	5.936	3.976**
Mf	24.951		26.849	4.276	1.107
Pa	18.064	5.943	13.057	5.726	2.630*
Pt	37.958	9.026	31.167	5.219	3.278**
Sc	39.681	13.049	34.543	11.562	2.177*
Ma	28.725	5.366	22.984	5.062	2.151*
Si	29.804	6.983	29.188	6.775	0.419

*: $p<0.05$, *: $p<0.001$

Table 3. Comparison of EEG findings of research and control groups

EEG findings	
Research group (n=15)	**Control group (n=10)**
1- 7 case normal EEG (I,III,IV,V,VII,VIII,Xth, cases)	1- Immature EEG (in 1st case)
2- Right temporal sharp wave (in, II,IX and XIIth, case)	2- Normal EEG (others)
3- Slow waves in posterior fields (immature EEG) (in VI and, XIVth, cases)	

This result was slightly higher than the control group, but was not singificant. As for minor physical anomalies, in one patient from the verapamil group with widespread defect in organicity testing, electrified hair and high palate was found. For NSS, the results are seen in table I. MPA and NSS scores were higher in the research group than the control group, but the differences were not significant.

In patients taking both treatments, coprolalia, irritability, hyperactivity, echolalia and echopraxia got better, beginning with the second week.

DISCUSSION

When the research and control groups are compared in relation to organicity, there was slightly higher findings of organicity in the research group (though not statistically significant), which is consistent with the literature proposing organic factors for TD etiology. In this study verapamil and nifedipine were not different from each other in relation the effects and side effects; which is consistent with literature [2,7,8,12-14,15-19].

In the literature [11-6,11-18]; there are 20-50 % EEG abnormalities and pathologic CT's (usually cortical and subcortical atrophy, ventricular dilatation) are found in 20 % patients. In our series no CT anomaly was detected while EEG abnormalities were seen in 25 % patients.

Also in the literature is 67 % organicity positivity in organicity test and NSS. This is also consistent with our findings [3-5,13,14].

In conclusion; significant improvement have been obtained from CCB's. On the other hand, clonidine, another alternative to haloperidol, has many side effects, while none of them can be seen with verepamil and nifedipine [12-14]. There is no significant differences between the two drugs. Consistent with the literature, these two drugs improved motor and vocal tics, decreased involuntary movements, irritability and compulsive symptoms in our patients [4,5,6,8-10,12,13,16,17,19]. In conclusion, we believe that TD is disorder caused by psychological and or-

ganic causes; with haloperidol being a good treatment under low doses, and with verapamil and nifedipine being good alternatives to haloperidol, should side effects of haloperidol be seen.

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