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LITHIUM-INDUCED TREMOR TREATED WITH VITAMIN B_6: A PRELIMINARY CASE SERIES

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ABSTRACT

Objective: The occurrence of tremor in patients receiving lithium is well known, but the management of this side effect is a significant problem both for patients and physicians. Although some reports have suggested that beta-blockers may be useful in treating lithium-induced tremor (LT), these agents have different side effects which limit the possibility of their use. Vitamin B_6 has been reported to be effective in treatment of patients suffering from different kinds of neuroleptic-induced movement disorders including parkinsonism and tardive dyskinesia. *Methods:* This report presents the results of a preliminary four-week open-label clinical trial of five patients who suffered from LT and who were treated with vitamin B_6 (900-1200 mg/d). The severity of tremor was assessed using the tremor subscale from the Simpson-Angus Scale (SAS) and Subjective Clinical Improvement Impression scale (SCII). *Results:* After the addition of vitamin B_6 to their treatment, according to the SAS scores four patients showed an impressive improvement until total disappearance of tremor. The subjective scale, on which the patients' scored their impression of clinical improvement, showed similar results. None of the patients suffered from any side effects attributable to vitamin B_6. *Conclusions:* The results suggest that vitamin B_6 may alleviate LT, double-blind controlled trials are needed to establish this effect.

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Key Words: lithium-induced tremor, vitamin B_6, parkinsonism

Tremor is a regular continuous and rhythmical involuntary oscillation of a body part. Different diseases and factors may be reasons for its appearance. Medications can be one of such factors, as indicated in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and defined as "Medication-Induced Postural Tremor" [1]. One such drug is lithium. Lithium-induced tremor (LT) is one of the most common adverse effects. According to DSM-IV, LT is "common, usually benign, but may cause social embarrassment, occupational difficulties, and non-compliance." Incidence of LT is in a wide range—from 4 percent to 65 percent [2]. Until now the mechanism of its appearance is unclear. The management of LT also is a significant problem for patients and a therapeutic conundrum for physicians. There are several reports that LT may be diminished by administration of beta-adrenoreceptor antagonists [3-7]. LT may be frequently accompanied by other extrapyramidal symptoms, which raise doubts about the exclusive responsibility of beta-adrenoreceptor mechanisms for this phenomenon [8-10].

In the last few years there have appeared several reports concerning the use of vitamin B_6 as a treatment for patients suffering from different kinds of neuroleptic-induced movement disorders including parkinsonism and TD [11-15]. Moreover, some authors in a double-blind study found an improvement of fine motoric movement during target shooting in marksmen after taking elevated dosages of vitamins B_1, B_6, and B_{12} [16]. To the best of our knowledge, this is the first report about vitamin B_6 as a treatment of lithium-induced tremor.

The current study reports on a preliminary open-label clinical trial of vitamin B_6 add-on therapy in five patients who suffer from LT.

PATIENTS AND METHODS

Five outpatients gave informed consent to participate in this open-label study. Using the DSM-IV criteria, all of them were diagnosed as having Bipolar Disorders [1]. The patients' characteristics are presented in Table 1. Patients were excluded if they sufferred from eating disorder, malnutrition, gastro-intestinal absorption disorders, and/or any avitaminosis. Also, none of them received any medication which can influence gastro-intestinal absorption. Serum pyridoxine levels were in the normal range. During the study all other medications were kept at fixed dose. In addition, all patients received oral vitamin B_6 (900-1200 mg per day). Although most bipolar patients were treated with combination of neuroleptics and lithium, we chose patients for this study who were treated only with lithium.

We assessed the patients' condition by two means: objective severity of LT was evaluated by rating from 0 to 4 on the tremor subscale from the Simpson-Angus Scale (SAS) [17]. The patients' subjective feelings about their symptom improvement was self-rated by the Subjective Clinical Improvement Impression scale (SCII). This scale is our modification of the Clinical Global Impressions (CGI) [18] based on a rating from 0 to 6 (the items included in this scale were: 0—very much improved; 1—much improved; 2—minimally improved; 3—no change;

Table 1. Clinical Characteristics of Patients Suffered from Lithium-Induced Tremor and Response to Vitamin B_6

Sex/ age	Diagnosis	Duration of illness (years)	Lithium dosage mg/day and serum lithium levels mEq/L	Duration of LT (months)	Maximum daily dose of vitamin B_6 mg/day	SCII (weeks)				SAS (weeks)				
						1	2	3	4	0	1	2	3	4
M/28	BPD	10	1800/0.9	6	1200	3	2	3	3	3	3	2	3	2
M/20	BPD	5	1200/0.8	5	1200	2	2	1	1	3	1	1	0	0
M/39	BPD	4	1200/0.9	8	900	1	1	0	0	2	1	0	0	0
F/29	BPD	8	1500/0.86	2	1200	2	2	1	1	2	1	1	0	0
M/27	BPD	5	1800/1.0	60	900	2	1	1	1	3	2	1	1	0
					Means on ratings	2	1.6	1.2	1.2	2.6	1.3	1	0.8	0.4

Note: LT = Lithium-Induced Tremor, BPD = Bipolar Affective Disorder, SCII = Subjective Clinical Improvement Impression, SAS = Simpson-Angus Scale.

4—minimally worse; 5—much worse; 6—the worst). The clinical response was evaluated by comparing the rating scores at baseline, before the vitamin B_6 treatment, to each subsequent weekly measurement point. Clinically significant improvement was defined as a reduction of at least 30 percent from baseline to week 4 on the rating scales.

RESULTS

The rating scales scores for each patient at each interval are presented in Table 1. According to the SAS scores four patients showed an impressive improvement until total disappearance of the tremor. Only one patient did not have any improvement. The subjective scale, in which the patients' scored their impression of clinical improvement, showed similar results. One patient reported near total recovery, another three patients reported much improvement, and only one patient did not feel any change. None of the patients suffered from side effects attributable to vitamin B_6. At the end of the study three patients tried to stop the treatment with vitamin B_6 but with dramatic return of the tremor exactly as it was in the beginning days. In those cases we restarted the treatment and again saw the same beneficial effect.

DISCUSSION

Until now the treatment of choice in lithium-induced tremor is beta-blockers (propranolol, atenolol, nadolol) [3, 5-7]. Beta-blockers are not totally benign in that they have many side effects and some of the patients have contraindications such as diabetes, peripheral vascular disease, asthma, and congestive heart failure, which limit their use.

Based on the literature about the positive effect of vitamin B_6 on neuroleptic-induced parkinsonism and tardive dyskinesia [12, 14, 15], we decided to try treating patients who suffered from lithium-induced tremor with vitamin B_6. These preliminary results support our assumptions about efficacy of this treatment.

The mechanism of the tremor caused by lithium is still unclear, as is the mechanism by which vitamin B_6 treatment may ameliorate it. Kane and colleagues [8] reported on 38 patients treated only with lithium who developed parkinsonian symptoms. Tyrer and colleagues explained the appearance of extrapyramidal side effects after treatment with lithium by selective blockade of dopamine receptors [9, 10]. These reports provide clues concerning the connection between lithium, tremor, and vitamin B_6.

Vitamin B_6 plays an important role in the biochemical processes involved in biosynthesis of neurotransmitters and enzymes responsible for extrapyramidal side effects [19-21]. Based on the theory that free radicals may induce

extrapyramidal symptoms [22, 23], vitamin B_6 has antioxidant properties that may help to ameliorate this movement disorder.

Our study has a number of limitations such as a small number of patients. It was an open-label study and the treatment period was very short. There is a need for further double-blind controlled trials to more rigorously test this effect.

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