Vitamin B_6 Treatment in Acute Neuroleptic-Induced Akathisia: A Randomized, Double-Blind, Placebo-Controlled Study

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Background: Treatment strategies for acute neuroleptic-induced akathisia (NIA) contain anticholinergic (antimuscarinic) agents, dopamine agonists, γ-aminobutyric acid (GABA)-ergic agents, β-blockers, benzodiazepines, and serotonin antagonists. Nevertheless, many patients who suffer from acute akathisia fail to respond to treatment. In earlier studies, vitamin B_6 was found to be effective in the treatment of neuroleptic-induced movement disorders. The purpose of this study was to evaluate the efficacy of vitamin B_6 in the treatment of acute NIA. This is the first report of B_6 as a treatment for NIA.

Method: This study was conducted in 2 mental health centers from February 2003 to November 2003. Twenty schizophrenia and schizoaffective inpatients with a DSM-IV diagnosis of NIA were randomly divided to receive vitamin B_6 600 mg/day b.i.d. (N = 10) or placebo (N = 10) twice a day for 5 days in a double-blind design. The Barnes Akathisia Scale (BAS), the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impressions scale (CGI) were used to assess the severity of NIA and psychotic symptoms. The BAS assessment was made at baseline and every day during the study. The BPRS and CGI were completed at baseline and at the end of the study.

Results: The vitamin B_6–treated patients in comparison with the placebo group showed a significant improvement on the subjective-awareness of restlessness ($p = .0004$), subjective-distress ($p = .01$), and global ($p = .004$) subscales of the BAS. The objective subscale did not demonstrate significant positive results ($p = .079$), but there was a trend of symptom amelioration in the vitamin B_6 group. A reduction of at least 2 points on the BAS global subscale was noted in 8 patients in the vitamin B_6 group (80%), and in only 3 patients in the placebo group (30%) ($p = .037$).

Conclusion: Our preliminary results indicate that high doses of vitamin B_6 may be useful additions to the available treatments for NIA, perhaps due to its combined effects on various neurotransmitter systems.

(J Clin Psychiatry 2004;65:1550–1554)

Received March 16, 2004; accepted June 7, 2004. From the Mental Health Center, Faculty of Health Sciences Ben-Gurion University of the Negev, Be'er-Sheva (Drs. Lerner, Statsenko, and Miodownik) and the Mental Health Center Tirat Carmel, Haifa (Dr. Bergman), Israel.

The authors report no financial or other affiliation relevant to the subject matter of this article.

The authors thank Tzvi Dwolatzky, M.D., of Be'er Sheva Mental Health Center for editorial assistance.

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Akathisia is determined by the DSM-IV as subjective complaints of restlessness accompanied by observed movements such as fidgety movements of the legs, rocking from foot to foot, pacing, or inability to sit or stand still. This phenomenon develops within a few weeks of starting or raising the dose of neuroleptic medications or after reduction of medications used to treat extrapyramidal symptoms.[1] The condition of inability to sit still was first described by Haskovec more than 100 years ago.[2] Now, the term is used exclusively for description of neuroleptic drug–induced irritability. Incidence rates for acute akathisia with conventional neuroleptics vary from 8% to 76%, with 20% to 30% as a conservative estimate.[3] Pathogenesis of akathisia still remains unclear. There are various theories regarding the development of akathisia. It seems now that imbalance of several neurotransmitter systems in tegmental and nigrostriatal areas may be involved in the pathogenetic process. This process includes dopamine, norepinephrine, acetylcholine, γ-aminobutyric acid (GABA), and serotonin systems.[4,5] Treatment strategies for akathisia contain anticholinergic (antimuscarinic) agents, dopamine agonists, GABAergic agents, β-blockers, benzodiazepines, and serotonin antagonists.[6–9] Nevertheless, many patients who suffer from acute akathisia fail to respond to treatment.

Several reports demonstrated that vitamin B_6 may be effective in the treatment of patients suffering from neuroleptic-induced movement disorders including parkinsonism, tardive dyskinesia, and lithium-induced tremor.[10–13] Although the mechanism of akathisia remains uncertain, and theories sometimes contradict each other, we decided to treat such patients with vitamin B_6. The rationale for

this decision was derived from our and others' experience of beneficial effect in treating neuroleptic-induced movement disorders with this agent. Furthermore, we had a positive empirical experience with vitamin B_6 in treatment of akathisia, which was demonstrated by a preliminary open study (not published).

The aim of the present preliminary study was to examine the efficacy of vitamin B_6 as a treatment for acute neuroleptic-induced akathisia (NIA). To the best of our knowledge, this is the first report of vitamin B_6 as a treatment for acute akathisia.

METHOD

Subjects

The study was conducted in 2 mental health centers from February 2003 to November 2003. Inclusion criteria for this study were (1) a DSM-IV–criteria diagnosis of acute NIA, (2) a score of at least 2 (mild akathisia) on the global subscale of the Barnes Akathisia Scale (BAS),[14] (3) an unchanged dose of all medications for at least 3 days before the baseline ratings and during the entire study period of 5 days, and (4) current hospitalization. Patients were not included if anticholinergic agents were started less than 10 days before screening. Furthermore, patients receiving β-adrenergic receptor antagonists or vitamin therapy were excluded.

Twenty inpatients (14 men and 6 women) were enrolled in the study. Their ages ranged from 21 to 69 years (mean age = 42.4 years, SD = 14.7). All patients received neuroleptic agents. Fourteen patients received conventional psychotropics (chlorpromazine equivalent 300–900 mg/day, mean ± SD dose = 438.6 ± 195.2 mg/day). Six patients (3 in the vitamin B_6 group and 3 in the placebo group) received atypical antipsychotics (3 patients, risperidone 4–8 mg/day, mean ± SD dose = 6.0 ± 2.0 mg/day, and 3 patients, olanzapine 10–20 mg/day, mean ± SD dose = 16.6 ± 5.8 mg/day). Eleven patients (6 in the vitamin B_6 group and 5 in the placebo group) were treated with combination therapy (antipsychotic and valproic acid [800–2000 mg/day, mean ± SD dose = 1314.3 ± 429.8 mg/day] or lithium [800–1200 mg/day, mean ± SD dose =1350.3 ± 173.2 mg/day]). Treatment with an anticholinergic agent (trihexyphenidyl), begun prior to the appearance of NIA to treat parkinsonian symptoms, was continued in 8 patients (4 in the vitamin B_6 group and 4 in the placebo group) at doses ranging between 2 and 6 mg/day (mean ± SD dose = 4.2 ± 1.3 mg/day). In these patients, NIA appeared and persisted in spite of this treatment. The mean time of unchanged dose medications before the study began was 12.3 ± 4.2 days.

The diagnosis of NIA was established by clinical interview. All patients developed akathisia just a few days after exposure to a new neuroleptic drug (Table 1). There was no relationship between the akathisia and psychotic irritability. Furthermore, the patients complained of a sense of being driven and an awareness of tension and discomfort in the lower limbs, one of the distinguishing criteria between akathisia and psychotic agitation.[14–16] The severity of akathisia was rated by the BAS[14] at baseline and every day during the study. All patients were assessed by the same investigators (J.B., N.S.), who underwent a pretrial training period. Because the study was conducted in 2 mental health centers, interrater reliability of raters on the BAS was examined: the κ was 0.89. Clinically relevant response was defined as a reduction of at least 2 points on the BAS global subscale. In addition, the Brief Psychiatric Rating Scale (BPRS)[17] and the Clinical Global Impressions scale (CGI)[18] were completed at baseline and at the end of the study. All assessments were made in the morning at the same time of day (8:00 a.m. ± 1:00 hour), before drug administration. All participants were physically healthy, and the results of routine laboratory tests were within normal range.

All patients gave their written informed consent after receiving detailed information about the study. The Institutional Review Board Ethics Committee of the hospital approved the study.

Study Design

The study design was double-blind and placebo-controlled. Twenty selected inpatients for this study were randomly divided to receive either vitamin B_6 600 mg/day b.i.d. (N = 10) or placebo (N = 10) twice a day for 5 days. Clinical and demographic characteristics of study participants are presented in Table 1.

The preparations were made by a professional pharmacist in the same size and color capsules in individual number-coded packages. The capsules were added to the patients' usual medications and were given by nurses. Both rater and patient were blind to the patients' drug assignment.

Statistical Analysis

Analysis of covariance (ANCOVA) with repeated measurements (analysis of variance [ANOVA] and multivariate ANOVA [MANOVA]), with the baseline values as covariates, was performed to detect between-group differences for the BAS subscale scores during the study period. Differences between groups in the demographic and baseline clinical data were compared with the χ^2 test, and baseline scores were analyzed with the Student t test. The scoring changes of the assessment scales during the trial period were statistically analyzed for each patient. The mean proportional change in scores (from baseline) was analyzed for each group. Response versus nonresponse according to the BAS was analyzed with the χ^2 test. Fisher exact test was also applied when expected frequencies were small. All tests were 2-tailed; $p < .05$ was considered significant.

Table 1. Demographic and Clinical Characteristics and Baseline Rating Scale Scores of Vitamin B_6 and Placebo Groups With Acute Neuroleptic-Induced Akathisia (N = 20)

Variable	Vitamin B_6	Placebo	p Value
Age, mean ± SD, y	36.2 ± 14.6	48.7 ± 12.4	.0538
Sex, male:female	9:1	5:5	.1432[a]
Duration of illness, mean ± SD, y	13.0 ± 21.2	8.2 ± 14.7	NS
Duration of akathisia, d			
Mean ± SD	11.1 ± 9.5	8.1 ± 14.9	NS
Range	4–23	2–27	NS
Diagnosis			
Schizophrenia	6	5	NS
Schizoaffective disorder	4	4	NS
Mood disorder	0	1	NS
Treatment			
Atypical antipsychotics	3	3	NS
Antipsychotics + valproate or lithium	6	5	NS
Antiparkinsonian drugs	4	4	NS
Baseline scores, mean ± SD			
Brief Psychiatric Rating Scale	50.2 ± 8.3	47.5 ± 7.8	NS
Clinical Global Impressions scale	4.7 ± 0.48	4.6 ± 0.51	NS
Barnes Akathisia Rating Scale			
Objective subscale	2.7 ± 0.48	2.5 ± 0.52	NS
Subjective subscales			
Awareness of restlessness	2.7 ± 0.48	2.4 ± 0.51	NS
Distress related to restlessness	2.5 ± 0.52	2.3 ± 0.48	NS
Global subscale	4.1 ± 0.73	3.8 ± 0.78	NS

[a]Yates corrected χ^2.
Abbreviation: NS = not significant.

RESULTS

All patients completed the trial. None suffered from any side effect. Since there was a significant difference between vitamin B_6 and placebo groups regarding age ($p < .05$) (Table 1), we performed repeated-measures ANCOVA with age as covariate and sex and time (the trial period) as grouping factors. This analysis showed no significant interaction between sex, time, and age ($F = 0.50$, $df = 5,90$; $p = .77$). The mean baseline BPRS and CGI scores did not differ between the groups. The mean baseline ratings for the BAS subscales also were similar. The mean changes from baseline in each of the BAS subscale scores and the BPRS and CGI scores are presented in Table 2. A significant difference between baseline and final rating on all scales was demonstrated. Ratings of the objective subscale showed a trend of improvement in the vitamin B_6 group, but it did not approach a significant level ($p = .079$). On the subjective subscales (awareness of restlessness and distress related to restlessness) and the global clinical assessment subscale, ANOVA/MANOVA showed a significant 2-way interaction of treatment and time. The subjective subscale showed that vitamin B_6 produced a greater reduction in NIA than did placebo (subjective-awareness of restlessness: $F = 5.07$, $df = 5,90$; $p = .0004$ and subjective-distress: $F = 3.2$, $df = 5,90$; $p = .01$). This beneficial effect was revealed from the third day (least significant difference post hoc test $p < .0004$ and $p < .009$, respectively). The same effect was obtained with the global subscale ($F = 3.74$, $df = 5,90$; $p = .004$) from the second day (least significant difference post hoc test $p < .05$).

As some patients were treated only with antipsychotics and others with a combination of antipsychotics and mood stabilizers (valproate and lithium), we compared these groups in order to examine whether there was an influence of the different treatments on the improvement of akathisia. ANOVA/MANOVA test revealed no significant difference between the groups ($p > .12$). We can suggest that vitamin B_6 ameliorated the akathisia signs but not the neuroleptic-induced dysphoria.

Furthermore, according to the definition of response as a reduction of at least 2 points on the BAS global assessment subscale, the number of responders was significantly greater in the vitamin B_6 group (8/10, 80%), than in the placebo group (3/10, 30%) ($p = .037$). A complete disappearance of NIA (BAS global score = 0) occurred in 3 patients (30%) in the vitamin B_6 group and in 1 patient in the placebo group (10%). Only 2 patients in the vitamin B_6 group showed nonsignificant clinical improvement on this scale (1 point on the global subscale), whereas in the placebo group there were 6 such patients, and the state of 1 patient remained unchanged.

The baseline BPRS scores of the vitamin B_6–treated patients showed a slight trend toward more severe psychotic symptoms compared with those of the placebo-treated patients. However, at the end of study, reduction in the BPRS scores in the vitamin B_6 group was significant in comparison with the placebo group ($F = 14.31$, $df = 1,18$; $p = .0014$).

In contrast to the baseline CGI scores of both groups, which were almost equal, the final scores also showed a significant improvement in the vitamin B_6 group in comparison with the placebo-treated patients ($F = 17.97$, $df = 1,18$; $p = .0005$).

DISCUSSION

The results of the present study show that the treatment of patients suffering from acute akathisia with vitamin B_6 led to improvement of NIA symptoms within a few days. In this study, neuroleptic-induced extrapyramidal effects were not measured, as our previous study results showed a beneficial effect of vitamin B_6 on these symptoms after only 2 to 3 weeks of treatment.[12,13]

Our analysis showed differences between the 2 groups regarding the patients' age and sex. These factors may be ignorable because most epidemiologic studies found no sex differences in the vulnerability to akathisia,[3] except for 1 study in which there were more females (41%) than males (20%) among psychiatric inpatients in a long-term unit who suffered from akathisia.[19] However, in this

Table 2. Effect of Vitamin B_6 and Placebo in Patients With Acute Neuroleptic-Induced Akathisia (N = 20)[a]

Scale	Group	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Statistic[b] F	df	p Value
Barnes Akathisia Rating Scale										
Objective subscale	Vitamin B_6	2.7 (0.48)	1.7 (0.67)	1.4 (0.96)	1.2 (0.79)	1.4 (1.26)	0.8 (0.92)	2.04	5,90	.0797
	Placebo	2.5 (0.52)	2.3 (0.48)	1.9 (0.57)	1.8 (0.79)	1.6 (0.97)	1.7 (0.82)			
Subjective subscales										
Awareness of restlessness	Vitamin B_6	2.7 (0.48)	1.9 (0.87)	1.1 (0.87)	1.0 (1.05)	1.2 (1.13)	0.7 (0.82)	5.07	5,90	.0004
	Placebo	2.4 (0.51)	2.2 (0.42)	2.1 (0.57)	2.2 (0.63)	1.9 (0.87)	2.0 (0.94)			
Distress related to restlessness	Vitamin B_6	2.5 (0.52)	1.7 (0.82)	0.9 (1.10)	0.7 (0.82)	0.8 (1.13)	0.6 (0.84)	3.20	5,90	.0105
	Placebo	2.3 (0.48)	2.1 (0.31)	1.6 (0.70)	1.8 (0.91)	1.3 (1.05)	1.6 (0.84)			
Global subscale	Vitamin B_6	4.1 (0.73)	2.8 (0.92)	2.2 (1.23)	1.7 (0.95)	1.6 (1.17)	1.2 (1.13)	3.74	5,90	.0040
	Placebo	3.8 (0.78)	3.4 (0.97)	3.0 (0.94)	2.9 (1.10)	2.3 (1.25)	2.6 (1.34)			
Brief Psychiatric Rating Scale[c]	Vitamin B_6	50.2 (8.3)	…	…	…	…	47.1 (8.4)	14.31	1,18	.0014
	Placebo	47.5 (7.8)	…	…	…	…	46.9 (6.7)			
Clinical Global Impressions scale[c]	Vitamin B_6	4.7 (0.48)	…	…	…	…	1.3 (1.34)	17.97	1,18	.0005
	Placebo	4.6 (0.51)	…	…	…	…	3.7 (1.16)			

[a]Results are expressed as mean (SD). Symbol: … = data not collected.
[b]Analysis of variance (ANOVA)/multivariate ANOVA 2-way interaction compared with placebo.
[c]The scale was completed at baseline and on day 5.

study there was no separation between acute and tardive akathisia. Furthermore, there was no suggestion of how to specify the vulnerable patients.[3]

Vitamin B_6 was found an effective treatment for movement disorders induced by different psychotropic agents.[10–12,20–22] The previous findings involved tardive movement disorders and lithium-induced tremor. These data show that vitamin B_6 could be a successful treatment in acute movement disturbances. We chose the high dose (1200 mg/day) of vitamin B_6 for NIA treatment on the basis of previous studies,[13,20,23,24] our present studies, and follow-up after some of our other patients for 3 years. The lack of a notable adverse effect of vitamin B_6 and its high efficacy justify the use of such a dose. Furthermore, use of high doses of vitamin B_6 (mean dose of 638.9 mg/day) even in children (mean age of 6 years 3 months) during 10 weeks did not show clinically significant side effects.[25]

The mechanism of its action is not clear, but pyridoxyl-5-PO_4, derived from dietary pyridoxine, serves as a co-factor in the enzymatic decarboxylation of dopa to dopamine[26] and other metabolic transformations.[27,28] In the nervous system, pyridoxine-dependent enzymes subdivide into 2 major categories: (1) transaminases and (2) L-amino acid decarboxylases. Some of these enzymes are responsible for the production of GABA, and others are involved in the synthesis of serotonin[27] and melatonin.[29] On the other hand, vitamin B_6 also takes part in oxidative reactions.[10,30]

Thus, one possible explanation for the effects observed in this study is that vitamin B_6 is an antioxidant and a free radical scavenger. Free radicals have been implicated in a variety of neuropsychiatric conditions, many of which are marked by the gradual development of psychopathologic symptoms and movement disorders.

Our preliminary results indicate that vitamin B_6, perhaps due to its combined effects on various neurotransmitter systems, may be a promising new treatment in addition to the present available medications for NIA. However, conclusions should be taken with caution due to the small number of patients, and, in our opinion, the study needs an independent replication.

Efficacy of vitamin B_6 shows that pathophysiology of acute NIA is heterogeneous, and probably there are various subtypes of acute NIA, which respond to different pharmacologic approaches.

The interpretation of the results of our present study should be considered in light of some methodological limitations, including a relatively small sample in each group, absence of an additional comparison group treated with propranolol or mianserin, and insufficient randomization (differences in age and sex).

Further studies with larger samples are required to determine whether vitamin B_6 is effective in patients with acute NIA who are resistant to anticholinergic agents, β-blockers, and benzodiazepines. Moreover, it is necessary to assess the relative efficacy of vitamin B_6 versus other anti-NIA agents, such as β-blockers and mianserin.

Drug names: lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), propranolol (Innopran, Inderal, and others), risperidone (Risperdal), valproic acid (Depakene and others).

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