Branched Chain Amino Acid Treatment of Tardive Dyskinesia in Children and Adolescents

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Background: A series of studies had demonstrated that deficient clearance of the large neutral amino acid phenylalanine was associated with tardive dyskinesia (TD), that the administration of the branched chain amino acids (BCAA) significantly decreased TD symptoms over placebo, and that the observed TD symptom reduction was significantly correlated with a diminished availability of phenylalanine to the brain of adult men with psychosis. As part of an initiative by the National Institute of Mental Health to expand the testing of treatments that were successful in adults to children and adolescents, the present pilot study was undertaken to test whether the BCAA would also reduce TD symptoms in children and adolescents. A 2-week trial of the BCAA was thus conducted in 6 children and adolescents (age range, 10.5–16.5 years) for the treatment of TD symptoms.

Method: A clinical diagnosis of TD was made in all subjects on the basis of a global score derived from the Simpson Abbreviated Dyskinesia Rating Scale. Subjects were videotaped for TD evaluation at baseline and after 1 and 2 weeks of BCAA treatment given in the form of a drink administered 3 times daily. TD symptom change over the trial period was evaluated by researchers blinded to the treatment status of the evaluation.

Results: TD symptom decreases were substantial in 5 of the 6 participants, ranging from 40% to 65%. Two of the subjects received an additional course of treatment, and further reductions in TD symptoms over those seen in the 2-week trial were observed.

Conclusion: The substantial symptom decrease and tolerability observed suggest the use of the BCAA formulation for the treatment of TD in children and adolescents and warrant further large-scale studies.

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Greater diversity in the expression of antipsychotic-induced dyskinesias is seen in children and adolescents than in adults treated with these drugs.[1–3] This increased diversity (and thus complexity) results partly from the greater use of antipsychotic agents in children and adolescents with nonpsychotic disorders than in adults, and the use of antipsychotic treatment periods that are generally more episodic and of shorter duration in children and adolescents.[4,5] As in adults, however, tardive dyskinesia (TD) has been reported in this young age group and is a cause for serious concern.[1,6–8] Further, while atypical antipsychotics hold promise for a lower future incidence of TD, they present a therapeutic dilemma based on reported health problems, such as hyperglycemia, and new and exacerbated cases of diabetes in adult and adolescent populations.[9–11]

A series of studies has demonstrated a significant association between a deficient clearance of the large neutral amino acid phenylalanine (the precursor of the large neutral amino acid tyrosine, which is the precursor of the amine neurotransmitter dopamine) and TD, starting with the definition of phenylketonuria (a hyperphenylalaninemia) as a risk factor for the disorder in the mentally retarded.[12] This finding led to studies in psychiatric patients in which men with extensive antipsychotic treatment histories and TD showed significantly decreased plasma clearance of administered phenylalanine, whether it was given in the form of a protein meal[13] or in a standardized (l00 mg/kg of body weight) pure powder form.[14] A complete TD remission was also seen 2 hours subsequent to a protein meal (19.6% of the protein in the form

of branched chain amino acids [BCAA]) ingestion in 21 of 46 TD patients.[15] Given these findings, a treatment potential for TD was seen in the BCAA, particularly since it is known that ingestion of these large neutral amino acids decreases plasma phenylalanine by stimulation of protein synthesis[16,17] and insulin release[18,19] and results in decreased levels of cerebrospinal fluid phenylalanine.[20,21] The BCAA were thus then administered to men with TD, and statistically and clinically significant decreases in TD symptoms were seen in both an open study[22] and a placebo-controlled trial.[23] In the placebo-controlled trial, a significant correlation was observed between the decrease in plasma phenylalanine levels and the decrease in TD symptoms.[23] The present trial, hoping to replicate these TD symptom decreases observed for men, was conducted as part of a National Institute of Mental Health initiative expanding the testing of medications in children and adolescents with psychiatric disorders.

METHOD

Subjects

The clinical trial was conducted at St. Agatha Home (SAH), a residential facility for children and adolescents that is under the auspices of the New York Foundling Hospital, with the care of the children and adolescents also administered by the Administration for Children's Services (ACS) of the City of New York.

Consent Process

Consent statements for the children and adolescents were obtained from parents or guardians and were approved by the ACS and the medical director of SAH. Each subject was also required to formally assent to study participation by signing a form that was read to them, and that they read in the presence of facility caretakers. These processes were approved and monitored by the Institutional Review Board of the Nathan Kline Institute for Psychiatric Research (NKI) of the New York State Office of Mental Health, Orangeburg, N.Y.

Study Exclusions

Subjects were excluded from participation (U.S. Food and Drug Administration Investigational New Drug [FDA IND] 40,382) for the conditions of diabetes or hypoglycemia, clinically significant abnormal thyroid values, history of malabsorption syndrome, pancreatitis, amyloidosis, pernicious anemia, history of acute or chronic renal disease, history of gout or family history compatible with gouty arthritis, known or suspected history of a disorder of amino acid metabolism, and known or suspected history of proliferative disease such as multiple myeloma. Hepatitis was considered an exclusion if the prestudy screen was positive for hepatitis C antibody, hepatitis B antigen, hepatitis B antibody, or hepatitis A antibody and showed an aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma-glutamyl transferase (gamma-GT) at 180 or above, or if the patient had such a positive hepatitis result and was experiencing unexplained flu-like symptoms for a period of 2 weeks. Pregnancy was an exclusion, and pregnancy tests were conducted. Subjects were also excluded from participation if there was not documented proof of antipsychotic treatment experience in their medical chart.

Health Monitoring Before, During, and Following the Trial

Pretrial and posttrial physical examinations (including complete blood cell count, SMAC, urinalysis) were conducted by the medical director at SAH. The medical director screened laboratory results for all subjects and allowed for study participation. Subsequent to the trial, pretrial and posttrial physical examinations and laboratory reports for the 6 subjects were reviewed by the medical director, who determined that no pretrial to posttrial physical changes were clinically significant.

A checklist was used to monitor patients for gastrointestinal complaints, and study nurses checked general medical (including vital signs) and psychological status 3 times a day, 7 days a week, over the 2-week treatment phase of the study. None of these 6 trial subjects reported any problems.

Treatment Trial Protocol

The BCAA treatment formulation (valine:isoleucine: leucine :: 3:3:4), as defined by the first author,[24] was administered at a dose of 222 mg BCAA per kilogram body weight. The formulation is manufactured as a powder (Scientific Hospital Supplies, Ltd., Liverpool, U.K.), which, when dissolved in 148 mL (5 oz) of water, creates a pineapple-flavored drink. The drink was administered 3 times a day (after breakfast and 1 hour before lunch and dinner), 7 days a week, by the NKI study nurses for the 2 weeks of the trial.

Efficacy Variable

A clinical diagnosis of TD was made by the first author using a mild-to-severe global score based on a subscale of items from the Simpson Abbreviated Dyskinesia Scale (ADS).[25] This criterion is identical to that used by other TD investigators[26] and has been described previously.[27] The study-dependent variable was a videotaped TD movement frequency count.[22,28] Subjects were videotaped for TD evaluation at baseline and after 1 and 2 weeks of BCAA treatment. Videotaped evaluations were rated blind by the first author subsequent to completion of the trial, in randomized time and subject order. Patients had 2 to 6 TD movements, each one videotaped for 4 minutes, and thus a minimum of 8 minutes of movements per patient were recorded at each evaluation; the total time

Table 1. Subject Characteristics

Subject	Age, y	Sex	Psychiatric Medication Use During Trial and Recent History
A	16.5	M	Risperidone 5 mg/d; fluoxetine hydrochloride 20 mg/d; lithium carbonate 300 mg/d
B	16.0	M	None; last neuroleptic use 146 d prior (haloperidol)
C	10.5	F	Lithium carbonate 900 mg/d; last neuroleptic use 123 d prior (thioridazine)
D	10.5	F	Chlorpromazine hydrochloride 125mg/d
E	12.5	M	None; last neuroleptic use 21 d prior (chlorpromazine hydrochloride)
F	12.0	M	Methylphenidate hydrochloride 20 mg/d for first 9 d in trial and 10 mg/d for remaining 5 d in trial; last neuroleptic use 143 d prior (thioridazine)

Table 2. Tardive Dyskinesia (TD) Symptom Change

Subject	Movement Site (number)[a]	Movement Counts Baseline	Movement Counts Week 2	TD Symptoms % Change
A	Tongue, lip, jaw	33	15	–54.55
B	Tongue, lip, jaw	61	106	+73.77
C	Tongue, jaw (2)	78	47	–39.74
D	Tongue, jaw, toes (2)	47	27	–42.55
E	Tongue, jaw, fingers (2), toes (2)	138	66	–52.17
F	Tongue, jaw	17	6	–64.71

[a]Number of different movements evaluated at that site.

counted per patient ranged from 8 to 24 minutes. The frequency counts were determined from the 4 minutes of videotaped observation per movement. The criterion for change was the difference between frequency counts of TD symptoms from the baseline evaluation to the evaluation at the end of 2 weeks of treatment. The percent change in movement counts was calculated as {[(counts after week 2–baseline counts)/baseline counts] × 100}.

Continuation Protocol

ACS required that the children from SAH who showed treatment response be offered the opportunity to continue in treatment. The SAH medical director conducted this continuation study and the nursing staff administered the treatment. A second consent form for the continuation was obtained, using the same process described for the original consent. Each child who showed a 50% or greater decrease in symptom levels in the 2-week trial was given the option of continuing in treatment if at all feasible. This opportunity was offered to subjects A and E who met the response criteria; they both agreed, consents were obtained, and both were entered into the continuation study. Subject F, although he met the criteria, was returning to his family soon after the 2-week trial was completed and thus could not participate in the continuation. There were no protocol-suggested restrictions on the medication regimen as prescribed by the treating psychiatrist.

RESULTS

Subject Characteristics

The group of 6 study subjects included 4 boys and 2 girls with a documented neuroleptic treatment history and a range of current medication regimens (Table 1). Two of the 6 subjects were receiving antipsychotic medication during the 2-week trial. Antipsychotics, lithium, and fluoxetine were kept at a constant dose from 2 weeks before study initiation until the completion of the trial. DSM-IV chart diagnoses[29] included 2 subjects with conduct disorder, 1 with pervasive developmental disorder with autism, 1 with attention-deficit/hyperactivity disorder combined type, 1 with schizoaffective disorder, and 1 with major depressive disorder with psychotic features.

TD Symptom Change During the Trial

As shown in Table 2, 5 of the 6 subjects that completed the trial demonstrated substantial decreases in TD symptoms, with 3 of the 5 showing a 50% or greater symptom decrease. Anecdotally, for subject A, we received reports from SAH cottage staff and teachers of improved focus and attention and diminished symptoms of stuttering along with the TD. In subject B, we saw a substantial worsening of TD symptoms during the 2 weeks of the trial.

Weight Gains During the Trial

Five of the 6 subjects showed weight gains from baseline to week 2 that ranged up to 2.58%. None of these subjects were obese or became obese, according to established age- and gender-specific body mass index criteria.[30]

TD Symptom Change in the Continuation Protocol

Two adolescent boys underwent subsequent longer treatment periods in the continuation protocol. Subject A received treatment for an additional 52 days and Subject E for an additional 88 days (although treatment was missed for 2 days in that period). Figures 1 and 2 demonstrate (1) the escalated treatment response in these longer treatment periods (Subject A, from 55% after 2 weeks to 97% response after 32 additional days; Subject E, from 52% after 2 weeks to 78% response after 56 additional days), and (2) that even after long intervals without treatment between the 2-week trial and the beginning of the continuation protocol (5 weeks for Subject A and 12 weeks for Subject E while approvals and consents were being obtained), neither subject had returned to the level of symptoms observed at baseline 1.

DISCUSSION

The BCAA treatment substantially reduced TD symptoms in 5 children and adolescents. Two boys who were

Figure 1. Subject A: Tardive Dyskinesia (TD) Movement Counts in the 2-Week Trial and Continuation Period of Branched Chain Amino Acids (BCAA) Treatment, Separated by a 5-Week Interval Without Treatment

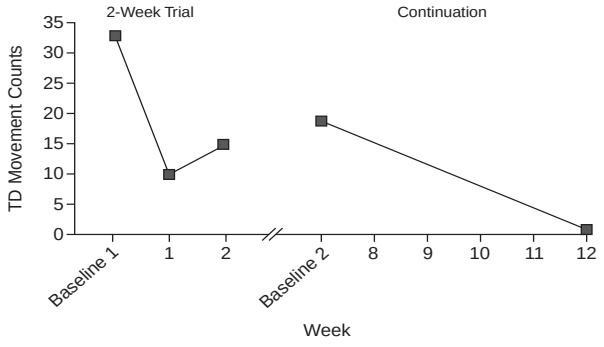
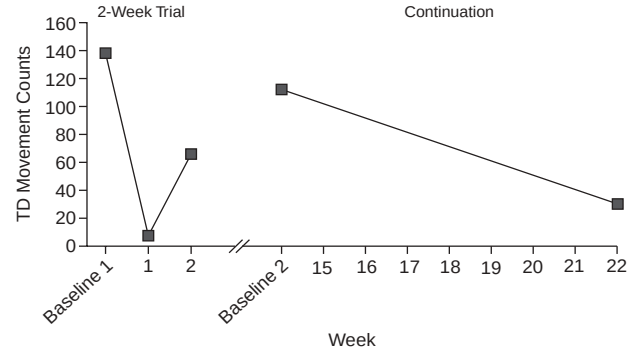


Figure 2. Subject E: Tardive Dyskinesia (TD) Movement Counts in the 2-Week Trial and Continuation Period of Branched Chain Amino Acids (BCAA) Treatment, Separated by a 12-Week Interval Without Treatment



evaluated at approximately 1 or 3 months after the 2-week trial maintained a level of TD symptom decrease compared with (first) baseline, indicating a lasting beneficial effect of treatment. There were further improvements seen with extended treatment periods in these 2 boys, suggesting that responsiveness to the BCAA persists and that treatment regimens longer than 2 weeks may be required for maximal efficacy.

One boy showed an increase in TD symptoms during the course of the study, which was not unexpected given the atypical pharmacology (compared with adult patterns) of neuroleptic-induced neurologic side effects seen in young patients, particularly in males, such as a negative relationship between TD expression and current use of benztropine.[7,31]

Earlier work had demonstrated an association of plasma phenylalanine indices (2-hour post oral phenylalanine ingestion plasma levels of phenylalanine and plasma phenylalanine/large neutral amino acid ratios) with TD in adult men but not in adult women,[14] thus suggesting that BCAA treatment may not alleviate TD in women. Gender differences in basal plasma phenylalanine levels that are apparent in adolescents and adults, however, are not evident in children, consistent with a response to hormonal influence in adolescence and adulthood.[32–34] In this study, improvements in TD symptoms were observed following BCAA administration to 2 girls (both aged 10 years), suggesting that the response to BCAA treatment in preadolescent girls is similar to that in male subjects.

The anecdotal decrease in stuttering for Subject A during BCAA treatment is consistent with the data demonstrating that (1) ingestion of the BCAA decreases plasma levels of phenylalanine and tyrosine, the precursors of dopamine, reducing the availability of these amines to the brain, and thus reduced central nervous system dopamine synthesis[20,21] and (2) stuttering is due to increased dopamine activity and has been treated effectively with antidopaminergic agents such as antipsychotics.[35,36] The BCAA formulation used in this study, therefore, may provide a more benign and perhaps equally effective alternative to antipsychotic drugs for the distressing symptom of stuttering.

In conclusion, our results suggest that the BCAA formulation tested may provide a safe and useful agent for treating TD symptoms in young persons requiring continuing antipsychotic drug therapy.

Drug names: benztropine (Cogentin and others), chlorpromazine (Thorazine, Sonazine, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), methylphenidate (Ritalin, Metadate, and others), risperidone (Risperdal), and thioridazine (Intensol).

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