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Prospective Open-Label Clinical Trial of Trihexyphenidyl in Children With Secondary Dystonia due to Cerebral Palsy

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Although trihexyphenidyl is used clinically to treat both primary and secondary dystonia in children, limited evidence exists to support its effectiveness, particularly in dystonia secondary to disorders such as cerebral palsy. A prospective, open-label, multicenter pilot trial of high-dose trihexyphenidyl was conducted in 23 children aged 4 to 15 years with cerebral palsy judged to have secondary dystonia impairing function in the dominant upper extremity. All children were given trihexyphenidyl at increasing doses over a 9-week period up to a maximum of 0.75 mg/kg/d. Trihexyphenidyl was subsequently tapered off over the next 5 weeks. Objective motor assessments were performed at baseline, 9 weeks, and 15 weeks. The primary outcome measure was the Melbourne Assessment of Unilateral Upper Limb Function, tested in the dominant arm. Tolerability and safety were monitored closely throughout the trial. Of the 31 children who agreed to participate in the study, 5 failed to meet entry criteria and 3 withdrew due to nonserious adverse events (chorea, drug rash, and hyperactivity). Three children required a dosage reduction because of nonserious adverse events but continued to participate. The 23 children who completed the study showed a significant improvement in arm function at 15 weeks ($P = .045$) but not at 9 weeks ($P = .985$). Post hoc analysis showed that a subgroup (n = 10) with hyperkinetic dystonia (excess involuntary movements) worsened at 9 weeks ($P = .04$) but subsequently returned to baseline following taper of the medicine. The authors conclude that scientific evidence for the clinical use of trihexyphenidyl in cerebral palsy remains equivocal. Trihexyphenidyl may be a safe and effective for treatment for arm dystonia in some children with cerebral palsy if given sufficient time to respond to the medication. Post hoc analyses based on the type of movement disorder suggested that children with hyperkinetic forms of dystonia may worsen. A larger, randomized prospective trial stratified by the presence or absence of hyperkinetic movements is needed to confirm these results.

Keywords: dystonia; anticholinergic; trihexyphenidyl

Cerebral palsy is a frequent cause of impaired movement in children. It represents a heterogeneous group of disorders with commonly recognized etiological antecedents and risk factors and established diagnostic categories. Virtually every classification scheme in cerebral palsy differentiates pyramidal or spastic from extrapyramidal cerebral palsy, of which dystonia is often a common feature. Based on traditional classification schemes, 70% of patients with cerebral palsy are considered to be primarily spastic, with an additional 15% classified as primarily dystonic. Recently, there has been increased awareness of a dystonic component in children previously classified as having spastic cerebral palsy.[1-3] Reduction of spasticity has been a major focus of the treatment of cerebral palsy (reviewed by Gracies et al[4,5]), yet in many cases, dystonia may be a more disabling impairment. Therefore, there is a need to identify and test treatments for dystonia in children with cerebral palsy.

Dystonia in children is defined as "a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements,

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abnormal postures, or both."[3] Careful clinical assessment of children with cerebral palsy is essential to identify the presence of dystonia or other movement disorders. The pathophysiology of dystonia in cerebral palsy is likely to result from multiple mechanisms. Encephalopathy of prematurity and perinatal hypoxic-ischemic encephalopathy are important causes of dystonia, rigidity, and athetosis. The developing basal ganglia of term and preterm infants are particularly vulnerable to acute perinatal asphyxia.[6-8]

Several medications have been used to treat dystonia in adults, with effectiveness determined by both etiology and dystonia severity.[9] Trihexyphenidyl is perhaps the most commonly used medication to treat dystonia in neurological practice and is one of the few validated treatments for dystonia.[10] In 1979, Fahn reported the results of an open trial followed by a randomized placebo-controlled trial in adults and children with dystonia from multiple etiologies, and he concluded that "children and adults differed in response to anti-cholinergic therapy. The children tended to respond favorably and with fewer adverse events. The adults had less benefit and less tolerance of the drug."[11(p1257)] In the 2 trials conducted by Fahn (1979, 1983), 71% and 61% of the children, respectively, showed moderate to drastic improvement compared to 19% and 38% of the adults in each of these trials. Further analysis of the results suggested that children with milder degrees of dystonia experienced greater improvements on trihexyphenidyl. Jabbari and coworkers[12] studied the response to trihexyphenidyl in 100 adult patients with movement disorders, using 2+ points on the Burke-Fahn-Marsden Scale[13] as indicative of functional improvement. Nearly half of those treated showed improvement, and the authors found that dystonias that were more tonic in nature, of shorter duration, and not accompanied by magnetic resonance imaging evidence of a specific brain lesion tended to respond more positively. Several other studies have presented similar results, others have documented potential side effects, and different medication doses and titration strategies have been explored.[14] Most recently, a retrospective study showed that early use of trihexyphenidyl may have significant benefits in cerebral palsy.[15]

The mechanism of action of trihexyphenidyl for treatment of dystonia is not known, although it is presumed to be related to central anticholinergic effects. Dystonia is associated with disorders of basal ganglia function, and the presence of large cholinergic interneurons in the basal ganglia suggests that inhibition of cholinergic neurotransmission could affect this region. Muscarinic acetylcholine receptor subtypes may coassociate with dopamine receptor subtypes on neurons that project to different regions of the globus pallidus,[16] which may explain the antiparkinsonian effects of anticholinergic medication. A similar mechanism could explain the benefit in cerebral palsy if there is injury to the substantia nigra resulting in reduced dopaminergic innervation.[17] In animal models of asphyxia, there is evidence of relative preservation of cholinergic interneurons in the striatum compared with the degree of injury to their postsynaptic targets and the degree of injury to dopaminergic neurons.[18,19] This suggests the hypothesis of a relative increase in cholinergic innervation to the remaining targets. By reducing cholinergic transmission, trihexyphenidyl may re-establish the balance between dopaminergic and cholinergic drive, thereby reducing dystonia.[19]

Despite the interest in this medication, no prospective study has been done that specifically addresses the use of trihexyphenidyl in cerebral palsy. We report the results of a prospective, open-label study.

Methods

Subjects

Children between the ages of 4 and 17 years with a diagnosis of cerebral palsy and dystonia affecting the dominant upper extremity were recruited through clinics at 7 US medical centers over a 2-year period. Children were diagnosed with cerebral palsy if they had a static encephalopathy with onset of symptoms prior to 2 years of age. Dystonia was diagnosed by the principal investigator at each site and confirmed by subsequent review of videotapes by the principal investigator at the lead site. Dystonia was required to be of sufficient severity that the child had difficulty performing common daily tasks. Children were required to have a Gross Motor Function Classification System (GMFCS[20]) rating of level 2, 3, or 4 and sufficient cognitive function to be able to perform the tasks needed for testing. Arm dominance was determined by parent report.

The dominant arm was tested because it was thought that impairment of the dominant arm is more likely to contribute to disability. We excluded children with the hemiparetic form of cerebral palsy, in whom the dominant arm would be expected to be unaffected. Therefore, all children in the study were classified as tetraplegic and dyskinetic cerebral palsy.

Subjects were excluded if they had

1. complete absence of voluntary movement in the affected hands, wrists, and elbows;
2. severe weakness in the dominant upper extremity (Medical Research Council strength grade <4);
3. passive range of motion at the hand, wrist, or elbow less than 80% of normal;
4. current use of medications for dystonia (anticholinergics, levodopa, baclofen, diazepam, tizanidine, tetrabenazine, reserpine, and others);
5. changes in their physical therapy regimen during the 15-week study;
6. prior use of trihexyphenidyl or other anticholinergic therapy for dystonia;
7. history of surgery on the dominant upper extremity or cervical spine;
8. botulinum toxin injection in the dominant upper extremity within 6 months prior to the baseline visit or at any time during the study;
9. current or prior implantation of an intrathecal baclofen pump, deep brain stimulator, or other device to treat dystonia or spasticity;

10. concurrent acute or chronic medical condition (such as frequent seizures, heart disease, or asthma) that could adversely affect motor performance or the safety of testing;
11. presence of diurnal fluctuations or other clinical signs and symptoms suggesting an inborn error of metabolism or a family history of dystonia suggesting a genetic dystonia;
12. history of allergic or adverse reaction to trihexyphenidyl or other anticholinergic medications;
13. current complaint of urinary retention requiring treatment; or
14. history of glaucoma or family history of glaucoma with onset before the age of 40 years.

Parents of all subjects signed written informed consent, and subjects who were able signed assent. Parents of subjects who were recruited after the implementation of federal Health Information Portability and Accountability Act regulations signed authorizations for use of data and videotapes. All forms were approved by the individual institutional review boards as well as by the Stanford University Institutional Review Board.

Baseline data collected for each subject included a medical and neurological history; review of neuroimaging scans, if available; physical and neurological examination performed by a site investigator; and vital signs.

Medication

Trihexyphenidyl liquid mixed at a dilution of 2 mg per 5 mL was distributed by a single pharmacy from a single manufacturer's lot. The dose and visit schedule were as follows:

Visit 0: Screening: within 28 days of the baseline visit
Visit 1: Baseline: start of week 1
Week 1: 0.05 mg/kg twice per day
Week 2: 0.05 mg/kg 3 times per day
Week 3: 0.1 mg/kg 3 times per day
Week 4: 0.15 mg/kg 3 times per day
Week 5: 0.20 mg/kg 3 times per day
Weeks 6, 7, 8, and 9: 0.25 mg/kg 3 times per day
Visit 2: Peak dose: 9 weeks ± 3 days (between 60 and 67 days) after baseline
Week 10 (tapering down starts): Start tapering dose: 0.20 mg/kg 3 times per day
Week 11: 0.15 mg/kg 3 times per day
Week 12: 0.10 mg/kg 3 times per day
Week 13: 0.05 mg/kg 3 times per day
Week 14: 0.05 mg/kg 2 times per day
Week 15: Discontinue medication
Visit 3: Washout: 15 weeks ± 3 days (between 102 and 109 days) after baseline

Subjects were instructed to take the medication at approximately 8 AM, noon, and 4 PM for 3 times per day dosing and at 8 AM and noon for twice per day dosing. Visits were scheduled to occur in the morning at the approximate time of the first daily dose, and subjects were instructed to wait to administer the dose until they arrived for their visit. Testing of the primary outcome measure started between 1 and 3 hours following the dose.

Adverse events were monitored by biweekly telephone calls. If nonserious adverse events occurred requiring a decrease in dose, subjects maintained the highest tolerated dose until week 9, then initiated the taper. In such cases, the subject might discontinue medication prior to week 15.

Measures

The primary outcome measure was the Melbourne Assessment of Unilateral Upper Limb Function,[21] performed on the child's dominant (preferred) arm. This test was selected because of the wide range of possible outcome levels (100-point scale) and the inclusion of motor tasks related to meaningful functions such as reaching, grasping, and self-care. The test was administered by a physical therapist or an occupational therapist. Tests were videotaped by an assistant according to the Melbourne videotape protocol, and videotapes were subsequently scored by the therapist who administered the test. All testers attended a training session at Washington University in St Louis prior to initiating the study. The scaled score was used, which takes a value between 0 (poor performance on all tasks) and 100 (perfect performance on all tasks).

Secondary outcome measures were the Burke-Fahn-Marsden Dystonia Scale,[13] the Barry-Albright Dystonia Scale,[22] the modified Ashworth Scale,[23-25] the Gross Motor Function Measure,[20,26] a drooling scale, rapid syllable repetition, rapid finger tapping, rapid hand pronation and supination, the Pediatric Outcomes Data Collection Instrument,[27] the Pediatric Quality of Life Scale,[28,29] and the Care and Comfort Scale. The Burke-Fahn-Marsden, Barry-Albright Dystonia, Ashworth, Gross Motor Function Measure, syllable repetition, and finger-tapping scales were performed by the examining therapist. The Pediatric Outcomes Data Collection Instrument, Pediatric Quality of Life Scale, and the Care and Comfort Scale were rated by 1 parent. The drooling scale was rated by both parents and examiners.

Syllable repetition was tested by asking the child to repeat "pa-ta-ka" 20 times as fast as possible. Finger tapping was tested by asking the child to tap the index finger of the dominant hand on the table 20 times as fast as possible. Pronation-supination was tested by asking the child to tap the table alternately with the palmar and dorsal surface of the dominant hand for 20 complete cycles as fast as possible. These tests were scored by measuring the total time required using a stopwatch.

Table 1. Study Subjects and Primary Outcome Measures

ID	Age	Sex	Hand	Pattern	Etiology	GMFCS	Baseline	Peak Dose	Washout
1	8	M	L	Dystonia	Prematurity, IVH	4	99	92	98
2	10	M	L	Dystonia, athetosis	Perinatal asphyxia	4	50	42	51
3	15	M	L	Dystonia, athetosis	Perinatal asphyxia	3	82	76	75
4	8	F	R	Dystonia, spasticity	Prematurity	4	74	86	83
5	9	F	L	Dystonia, athetosis	Kernicterus	3	75	73	74
6	15	M	R	Dystonia, athetosis	Unknown	2	44	39	60
7	4	F	L	Dystonia, spasticity	Prematurity	4	39	43	43
8	5	F	R	Dystonia, athetosis	Perinatal asphyxia	4	41	34	41
9	6	F	L	Dystonia, athetosis	Schizencephaly	2	85	78	78
10	6	M	L	Hemidystonia, spasticity	Perinatal asphyxia	3	80	78	79
11	8	M	R	Dystonia, spasticity	Schizencephaly	2	84	92	95
12	7	M	R	Dystonia, spasticity	Prematurity	4	70	77	84
13	7	F	L	Dystonia, spasticity	Prematurity	4	43	49	49
14	9	M	L	Dystonia, spasticity	Prematurity	4	61	61	64
15	6	M	L	Dystonia	Near drowning	4	77	88	89
16	7	M	L	Dystonia	Perinatal asphyxia	4	87	90	95
17	8	M	L	Dystonia, spasticity	Unknown	4	14	5	9
18	9	F	L	Dystonia, spasticity	Perinatal asphyxia	4	29	32	29
19	4	F	R	Dystonia	Perinatal asphyxia	3	51	49	57
20	9	M	L	Dystonia	Perinatal asphyxia	4	53	58	60
21	9	F	R	Dystonia, spasticity	Unknown	3	1	0	0
22	8	F	R	Dystonia, spasticity	Perinatal asphyxia	4	37	29	30
23	10	M	R	Dystonia	Unknown	4	9	13	10

NOTE: GMFCS = Gross Motor Function Classification System; IVH = intraventricular hemorrhage.

Statistical Analyses

Change scores between visits 2 and 1 and between visits 3 and 1 were computed for all outcome measures. Calculations were done using Matlab (Mathworks Inc, Natick, Mass). The significance of change scores was measured using a *t* statistic if normality assumptions were verified by the Lilliefors test; otherwise, the nonparametric sign rank *U* statistic was used. The significance level for the primary outcome measure was .05. The significance level for the secondary outcome measures was .05 after Bonferroni correction for multiple (12) comparisons.

The protocol was submitted to the clinicaltrials.gov database (NCT00122044).

Results

Enrollment

Thirty-one children were enrolled. Five children did not initiate the study because of failure to meet criteria during the baseline visit examination. Three children subsequently withdrew because of adverse events. Twenty-three subjects completed the study, and their data were analyzed (see Figure 1). The characteristics of the study subjects are summarized in Table 1.

Adverse Events

Medication-related adverse events are listed in Table 2. No serious adverse events (life threatening or requiring hospitalization) related to the study medication occurred. Three children withdrew from the study because of adverse events: 1 child developed severe and uncontrollable chorea within days of starting the lowest dosage, 1 child developed a medication rash, and 1 child developed hyperactivity. All side effects resolved after stopping the medication and withdrawal from the study. Three children who remained in the study were unable to achieve the maximum target dose. One developed involuntary fist clenching, 1 developed increased fatigue and exercise intolerance, and 1 developed blurred vision. Eight subjects developed mild symptoms that did not require a change in the medication dose.

Primary Outcome

There was a significant improvement (increase) in Melbourne scores between visit 1 (baseline) and visit 3 (washout; mean change = 2.97, SD = 6.69, confidence interval = 0.07 to 5.86, $P = .045$, *t* test) but not between visit 1 and visit 2 (peak dose; mean change = –0.03, SD = 6.44, confidence interval = –2.81 to 2.76, $P = .99$, *t* test) (see Figure 2). There was no correlation between the change in Melbourne score and age, sex, handedness, or baseline Melbourne score.

Secondary Outcome

After correction for multiple comparisons, the only significant change in secondary outcome measures was a decrease in drooling at both peak dose (change = 1.24, SD = 1.30,

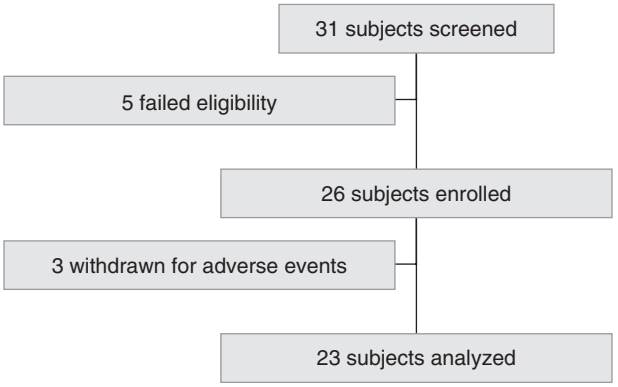

Figure 1. Study flowchart.

Table 2. Adverse Events

Symptom	n
Arm/hand stiffness	3
Emotional lability	2
Dry mouth	2
Chorea	1
Rash	1
Hyperactivity	1
Nausea	1
Night restlessness	1
Fatigue	1
Soft stools	1
Blurred vision	1

$P < .012$, sign rank test) and washout (change = 1.23, SD = 1.48, $P = .024$, sign rank test) visits compared to baseline. The peak dose Pediatric Quality of Life Scale total score ($P = .023$ before correction) and Care and Comfort personal scale score ($P = .007$ before correction) were significant by themselves, but they did not remain significant after correction for multiple comparisons.

Subitems

Analysis of individual items on the Melbourne showed that only item 32 (mean = 0.30, SD = 0.56, $P = .031$, sign rank test) was independently significantly different between washout and baseline visits. Therefore, it is unlikely that the overall improvement on the Melbourne can be attributed to only a single subitem.

Analysis of individual items on the Pediatric Quality of Life Scale showed that fatigue improved at peak dose (mean = –0.65, SD = 0.64, confidence interval = –0.93 to –0.36, $P < .033$ after correction for multiple [33] comparisons by t test) and washout visits (mean = –0.52, SD = 0.60, confidence interval = –0.79 to –0.25, $P = .033$ after correction). No other subitems of the Pediatric Quality of Life Scale, Pediatric Outcomes Data Collection Instrument, Care and Comfort Scale, or Gross Motor Function Measure were independently significant after correction.

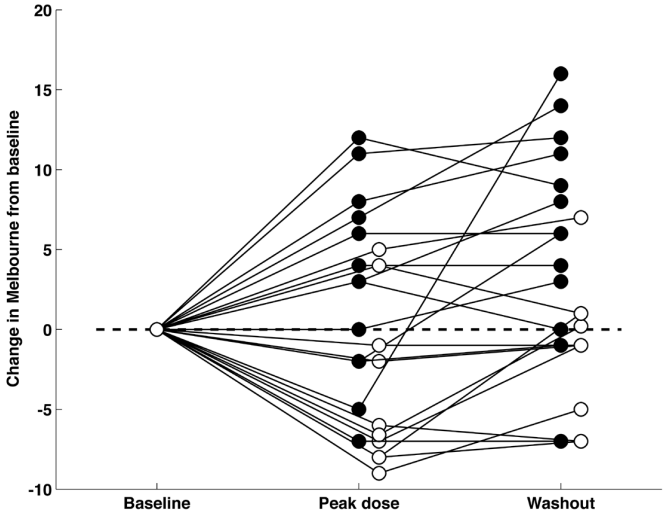

Figure 2. Change in the primary outcome measure for each subject, compared with values at the baseline visit. Children rated as hyperkinetic in the post hoc analysis are shown with open circles; children rated as nonhyperkinetic are shown with filled circles.

Post Hoc Subgroup Analysis

Because 1 child with excessive involuntary movements developed chorea and was withdrawn from the study, the principal investigator examined videotapes of all children in the study. This examination suggested several of the children who worsened on medication had hyperkinetic (increased involuntary) movements at baseline. Therefore, we investigated post hoc whether hyperkinetic features might be an independent predictor of poor response. One investigator at each site was asked to answer the question, "Does the subject have any hyperkinetic features? (Chorea, choreoathetosis, athetosis, or ballism?)" for each subject seen at that site, based on knowledge of the subjects or review of records and videotapes. Of the 23 children who completed the trial, 10 were rated as having hyperkinetic features. Analysis of this subgroup showed a significant worsening of Melbourne scores at the peak dose visit (mean = –3.86, SD = 5.11, $P = .037$, by sign rank test) but return to baseline at the washout visit. Analysis of the remaining (nonhyperkinetic) 13 subjects showed significant improvement at washout (mean = 6.23, SD = 6.48, confidence interval = 2.31 to 10.15, $P = .005$, by t test) but not at peak dose ($P = .10$, t test). Comparison by linear mixed-effects model showed a significant effect of group at both peak dose ($P = .006$) and washout ($P = .002$). Analysis of the secondary measures did not reveal any new significant findings.

Discussion

We have presented the results of the first prospective trial of trihexyphenidyl in children with secondary arm dystonia due to cerebral palsy. The results showed benefit at 15 weeks but not at 9 weeks. Some children showed improvement at 15 weeks compared to both 9 weeks and baseline. The most likely explanation for these observations is that the benefits of trihexyphenidyl require prolonged treatment, do not become detectable on the Melbourne scale until after 9 weeks, and persist during the 5 weeks of taper. This explanation matches clinical experience, in which children often will not respond to trihexyphenidyl until after weeks or months of treatment. We cannot exclude the alternative possibility that performance on the outcome measure improved with repeated practice. We also cannot exclude the possibility that baseline function improved during the 15 weeks of the study because of developmental processes and therefore that the effect was due to time rather than the medication. However, this seems less likely given the static nature of the disorder, the lack of change in therapy regimen, and the test-retest reliability of the Melbourne.

The subgroup analysis suggests the hypothesis that children with hyperkinetic features may not benefit or may actually worsen during treatment with trihexyphenidyl. This finding has been noted by experienced clinicians in several centers, and it emphasizes the importance of careful scrutiny for the presence of underlying hyperkinetic features when deciding on the use and dosage of trihexyphenidyl. However, it is important to realize that this subgroup was selected post hoc based on observation of the results. Therefore, a controlled trial with stratified recruitment into hyperkinetic and nonhyperkinetic subgroups is needed to test this hypothesis.

Our results are in agreement with previous studies of trihexyphenidyl. Fahn[11] studied children and adults with dystonia. His population included 4 children with birth injury, 3 of whom showed improvement on trihexyphenidyl. Marsden and colleagues[30] also reported experience with trihexyphenidyl in a retrospective study that included 5 children with secondary dystonia. The only published prospective randomized trial tested a total of 31 subjects, of whom 16 were younger than 18 years.[31] Two of these cases were due to birth anoxia and 1 case to encephalitis in the first year of life. These results are consistent with our findings, but the small number of children with secondary dystonia who have been previously tested in prospective trials underscores the importance of the current trial and the need for future randomized trials in this population.

This was an open-label, uncontrolled pilot study, and the possibility of a placebo effect due to lack of blinding of either the subjects or the examiners must be acknowledged. Although we did not observe any severe adverse events, we urge continued caution and close observation of patients treated with high doses of trihexyphenidyl. The purpose of this pilot trial was to determine effective doses, evaluate side effects, and evaluate the Melbourne scale as a candidate outcome measure. Confirmation of the efficacy of trihexyphenidyl for treatment of secondary dystonia in children with cerebral palsy will require a randomized controlled clinical trial, with consideration of subtypes and etiology of dystonia as determinants of treatment effect.

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Appendix

The Child Motor Study Group is dedicated to performing research trials to discover the best current and future treatments for childhood motor disorders. We acknowledge its current, past, and future members for their efforts on behalf of children with motor disabilities.

Members of the Child Motor Study Group

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