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Use of Trihexyphenidyl in Children With Cerebral Palsy

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A paucity of information exists regarding medications to treat dystonia in children with cerebral palsy. This study sought to review the benefits and tolerability of trihexyphenidyl in children with cerebral palsy, treated for dystonia or sialorrhea or both in a pediatric tertiary care hospital, through a retrospective chart review. In total, 101 patients (61 boys and 40 girls) were evaluated. The mean age at drug initiation was 7 years and 10 months (range, 1-18 years). The mean initial dose was 0.095 mg/kg/day. The dose was increased by 10-20% no sooner than every 2 weeks. The mean maximum dose reached was 0.55 mg/kg/day. Ninety-three patients (91%) tolerated the medication well, with a mean duration of treatment of 3 years and 7 months. Side effects occurred in 69% of subjects, the majority in patients aged ≥7 years, and soon after treatment initiation. Sixty-four percent continued the treatment at study end. Ninety-seven patients reported benefits, including reduction of dystonia in upper (59.4%) and lower (37.6%) extremities, sialorrhea (60.4%), and speech issues (24.7%). The majority of patients tolerated trihexyphenidyl well on a schedule of gradual dose increases, and almost all demonstrated improvements in dystonia or sialorrhea or both.

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Introduction

Cerebral palsy is the most common neurologic cause of impaired mobility in children. Fifteen percent to 25% of patients with cerebral palsy are estimated to present with dystonia [1] as a component of their motor disorders. Dystonia can cause functional impairment because of involuntary muscle contractions affecting the extremities, and is frequently associated with altered speech articulation, abnormal swallowing, and excessive drooling [2].

Although trihexyphenidyl has been used extensively in adults with movement disorders such as dystonia for more than 20 years, information is limited regarding the use of trihexyphenidyl in children. Evidence indicates that trihexyphenidyl may reduce the severity of dystonia [3-6].

The current options for the medical management of generalized dystonia in children with cerebral palsy are very limited, and are restricted to anticholinergics such as trihexyphenidyl or dopamine agonists [7]. As an anticholinergic, trihexyphenidyl also has a potential role in the treatment of sialorrhea, which affects 10-58% of children with cerebral palsy [8,9].

This study sought to review the clinical experience of the use of trihexyphenidyl in children with cerebral palsy for dystonia or sialorrhea or both, with special emphasis on benefits and tolerability.

Patients and Methods

A retrospective chart review was performed of all children with a diagnosis of cerebral palsy treated with trihexyphenidyl for dystonia or sialorrhea or both by the principal investigator (M.R.D.) over a 3-year period at the neurology outpatient clinic in a pediatric tertiary care hospital.

Data collected from medical records included demographic information, classification of cerebral palsy, comorbid conditions, concomitant treatments and medications, age at initial treatment with trihexyphenidyl, initial and maximum dose of trihexyphenidyl, dose adjustments, duration of treatment, reason for discontinuation, side effects, and tolerability and benefits of the medication as stated by parents/caregivers and members of the medical team.

For a statistical comparison of continuous variables that could be associated with the development of side effects, two-sample *t* tests were run (i.e., age at initiation and age at first reported side effects, and dose and duration of treatment with trihexyphenidyl). To identify an age group at

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greater risk of presenting with side effects, a χ^2 test was used. To determine if a difference existed between mean maximum doses of trihexyphenidyl in patients with one side effect, multiple side effects, and no side effects, one-way analysis of variance was used, with Tukey multiple comparisons if a significant analysis of variance F-statistic was obtained. The Fisher exact test was used to seek a correlation between side effects and trihexyphenidyl formulation (liquid or tablets), and logistic regression analysis was used to examine if a combination of factors could predict the occurrence of undesirable events. The relationship between age at onset of treatment and duration of treatment was evaluated using the Pearson correlation coefficient. $P < 0.05$ was considered statistically significant. The analyses in this study were generated using SAS/STAT software, version 9.1.3 (SAS, Inc., Cary, NC). This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

Results

In total, 101 patients with cerebral palsy, aged 1-18 years, were treated with trihexyphenidyl during the study period. Sixty-one boys and 40 girls were included. Type of cerebral palsy according to distribution of weakness included: 62% quadriparesis, 22% hemiparesis, 8% diparesis, 6% triparesis, and 2% paraparesis. Other comorbid conditions were present in 74% of the children, including epilepsy (46.5%), developmental delay (31.6%), constipation (32.6%), and others (37.6%). The majority of patients (94%) were receiving other treatments (Table 1). Oral management for spasticity (baclofen, diazepam, and tizanidine) was reported in 37.6% of children, and 38.6% had a history of botulinum toxin A injections.

Indications for treatment were dystonia in 28.7%, sialorrhea in 5.9%, and both dystonia and sialorrhea in 65.4%. The mean age at trihexyphenidyl initiation was 7 years and 10 months (range, 1-18 years) (Fig 1), with a mean initial dose of 0.095 mg/kg/day (range, 0.01-0.414 mg/kg/day), equally dividing the dose twice a day. Trihexyphenidyl was gradually increased in increments of 10-20% no sooner than every 2 weeks until a benefit or intolerable side effects occurred. Dose reductions were implemented if intolerable side effects occurred. The mean maximum dose of trihexyphenidyl during the study period was 0.55 mg/kg/day (range, 0.03-3.13 mg/kg/day), dividing the dose two or three times a day (Fig 2). All patients were seen in clinic every 3-4 months, and families received follow-up telephone calls every 2 weeks to monitor their treatment.

Table 1. Concomitant treatments in children with cerebral palsy undergoing treatment with trihexyphenidyl

Treatment	Number of Patients (n = 95)
Antispasticity	38
Botulinum toxin A	39
Antiepileptic	46
Psychiatric	14
Laxatives	46
Other*	11

* Other medications included gastrointestinal, asthma-allergy, analgesics, hormonal, supplements, or antibiotics.

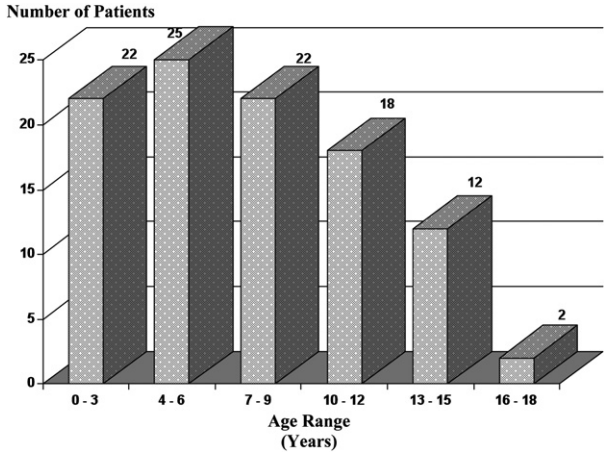

Figure 1. Age at initiation of treatment with trihexyphenidyl in children with cerebral palsy.

Side effects were reported in 69.3% of patients at some point during the study. The most frequent undesirable effect was constipation (42.6%), which had been a preexisting complaint in 27%. Other undesirable effects included decreased urinary frequency (18.8%), behavioral changes (12.9%), and excessive dry mouth (6.9%) (Table 2). Four children with choreoathetosis reported an increase in involuntary movements. No patients required hospitalization or emergency management because of side effects.

Complete information regarding side effects and the dose at which they occurred was available for 73% of patients. Forty-four percent of patients developed their first side effect at doses lower than 0.4 mg/kg/day (Fig 3). A significant difference in duration of treatment with trihexyphenidyl was evident, with a shorter time associated with the occurrence of a side effect (3.32 ± 2.36 months vs 1.48 ± 1.87 months, $P = 0.0005$), which remained significant after logistic regression analysis was performed ($P = 0.001$). Although the percentages of children who reported side effects at ages 7-12 years (22.3%) and age 13 years or

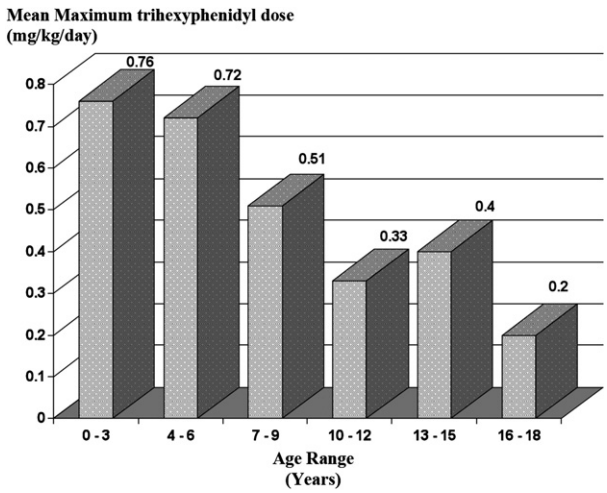

Figure 2. Mean maximum dose of trihexyphenidyl in children with cerebral palsy according to age group.

Table 2. Side effects of trihexyphenidyl in children with cerebral palsy

Side Effect	Number of Patients (n = 70)
Constipation	43
Decreased urinary frequency	19
Behavioral	13
Dry mouth	7
Blurred vision	5
Increased involuntary movements	4
Decreased seizure control	4
Delusions/hallucinations	2
Other	5

older (26.5%) were higher than for those aged less than 7 years (18.4%), statistical significance was not achieved.

Despite the high incidence of side effects, trihexyphenidyl was well tolerated in 91% patients. The mean duration of treatment was 3 years and 8 months (range, 0-10.8 years). No correlation was evident between duration of treatment and age at the beginning of medication ($-r = 0.02$).

Treatment was discontinued in 8% of children because of intolerable side effects. These included constipation (n = 2), other gastrointestinal signs (n = 4), behavioral problems (n = 2), increased involuntary movements (n = 1), drowsiness (n = 1), and skin rash (n = 1). All side effects resolved after discontinuation of the medication. Other reasons to discontinue treatment included lack of effect over time (8.9%), poor compliance (5.9%), placement of a baclofen pump (3.9%), and others (8.9%). Thirty-six patients (35.6%) eventually discontinued trihexyphenidyl during the study period. The mean treatment duration in this subgroup was 2 years and 10 months.

From data reported by parents/caregivers or members of the medical team, 96% of children demonstrated benefits of treatment with trihexyphenidyl. A reduction in dystonia in the upper (59.4%) and lower (37.6%) extremities was evident. Sialorrhea was reduced in 60.4% of patients. Other benefits included improvements in fine motor skills (39.6%), speech (24.7%), positioning (19.8%), ease of care (15.8%), toe walking (2.97%), and others (19.8%).

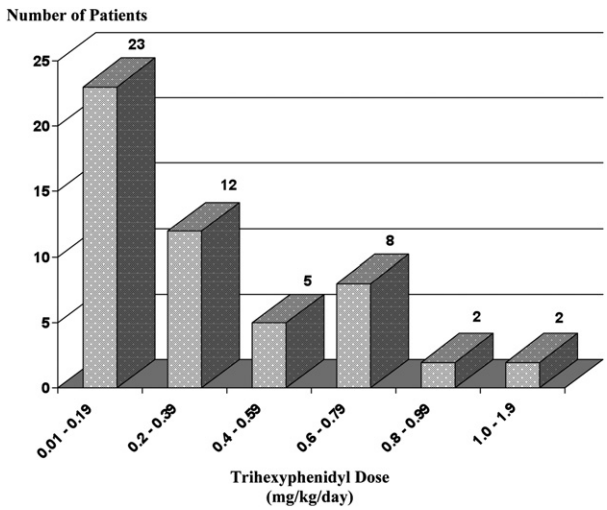

Figure 3. Lowest dose during development of side effects of trihexyphenidyl in children with cerebral palsy.

Discussion

Awareness of a dystonic component of motor disorders in children with cerebral palsy is rising, and is probably a contributory factor to unexpected outcomes of managing spasticity. In fact, dystonia can be more disabling than spasticity in some patients because it is triggered or increased by attempted voluntary movements, interfering with fine and gross motor activities, communication, and ease of care.

The pathophysiology of dystonia involves a dysfunction in the basal ganglia. The current model of basal ganglia function is based on two pathways from the cortex to the striatum, globus pallidus, thalamus, and back to the cortex: a "direct" pathway with primarily D1-like receptors, and an "indirect" pathway with primarily D2-like receptors. These pathways may work as positive (direct) and negative (indirect) feedback loops in which different neurotransmitters exert differential effects at distinct levels of the system. In general, overactivity of the indirect pathway is thought to produce dystonia [10], and this overactivity could be a consequence of an imbalance between dopaminergic and cholinergic systems. Therefore, it may respond to treatments that increase dopamine (e.g., L-dopa) or decrease acetylcholine (e.g., trihexyphenidyl) [2]. Recent theories postulate that after hypoxic-ischemic injury, the striatal cholinergic system seems to be preserved or upregulated, as supported by findings of an increase in cholinergic fibers and cell bodies and acetylcholine release [11]. Nonetheless, the precise role of acetylcholine in the pathophysiology of dystonia is still being studied. Large, aspiny neurons in the striatum produce this neurotransmitter, which exerts an inhibitory effect on the direct pathway by acting on M_3 (hyperpolarizing) receptors, but an excitatory effect on the indirect pathway through its action on M_1 (depolarizing) acetylcholine receptors [10]. In some patients with a dysfunctional system, the balance between both actions could lead to an increased inhibitory effect on the direct pathway, reducing activation on the internal globus pallidus, in turn causing a disinhibition of thalamocortical projections, and resulting in dystonic postures. Trihexyphenidyl could then restore, at least to some extent, the balance between both pathways and reduce dystonic postures.

Trihexyphenidyl has been used in adult patients with primary and secondary dystonia, with beneficial results in 37-41% of patients, at a mean dose of 21.5-36 mg/day (range, 4-130 mg/day) [4, 6,12]. A major limitation to the use of trihexyphenidyl in the adult population is the high frequency of intolerable side effects (30-68%), leading to treatment discontinuation [4,6,12]. Limited information is available regarding the use of trihexyphenidyl in children.

This series constitutes the largest, to the best of our knowledge, of treatment with trihexyphenidyl in children with dystonia secondary to cerebral palsy. In this study, trihexyphenidyl was well tolerated in the majority of children (91%), and none developed serious side effects, even at larger doses, consistent with other studies [3-6,13,14]. The most frequent side effects were constipation, decreased urinary frequency and salivary secretions, as well as behavioral changes. The majority of side effects was mild and transient, and resolved when the dose was adjusted.

Factors such as age, dose, concomitant treatments, and trihexyphenidyl formulation failed to demonstrate an association with the development of side effects in this study group. An individual threshold may act as the determinant for their occurrence. If this hypothesis is valid, a patient taking trihexyphenidyl could present an undesirable episode at any time while increasing the dose, more likely earlier rather than later. This outcome would be in accordance with the relationship between a shorter duration of treatment and the presence of side effects.

Although not statistically significant, a trend toward a decreased incidence of side effects in younger patients was evident in this study, as previously reported by others [3,4,6]. The number of patients in the older age group (10-18 years) may not have been sufficient to achieve statistical significance. The major difference in tolerability may be observed when comparing adults with children [3,4,6]. Unfortunately, information about the development of undesirable effects to trihexyphenidyl as our group entered adulthood is not available.

The high tolerability of this medication in children was confirmed recently in a prospective open label trial by Sanger et al. [13], using a higher mean maximum dose than in our study (0.75 mg/kg/day vs. 0.55 mg/kg/day, respectively). One of their patients with hyperkinetic features discontinued treatment because of worsening involuntary movements upon the initiation of trihexyphenidyl. This phenomenon was also evident in four patients in the present report, leading to discontinuation of the medication in one patient.

Most patients (96%) reported benefits from treatment with trihexyphenidyl, including a reduction in dystonia (primarily in the upper extremities), a decrease in excessive drooling, and an improvement in expressive language skills. This selective response was observed by others [5].

Our high rate of response may be attributable to the retrospective nature of this study. Fahn [4] reported that 61% of his pediatric population (n = 23) demonstrated at least moderate improvements in dystonia during an open label trial with trihexyphenidyl. Similarly, Marsden et al. [6] reported a reduction in dystonia in 52% of 23 children, and the response was independent of age of onset, age of initiating therapy, severity of dystonia, or etiology. In a double-blinded, crossover, randomized, controlled trial in 16 children and 15 adults with primary and secondary dystonia (age range, 9-32 years), Burke et al. [3] demonstrated a positive response in 71%, compared with placebo.

The effect of trihexyphenidyl in this study appeared to be sustained, because the mean duration of treatment was 3 years and 8 months, and 64% of patients continued using the medication for more than 3 years. This finding was reported by others [3,6]. Although other authors [3,5] suggested that trihexyphenidyl therapy may be more effective when initiated early in the course of the disease, this study failed to support that correlation, using age at treatment onset and duration of treatment as indicators of continued efficacy.

The beneficial effects of trihexyphenidyl may take some time to appear [3,6,13]. This delay may explain why significant functional improvement was not evident in a recent study where measurements were performed only 12 weeks after initiating treatment [14].

Excessive drooling in cerebral palsy population is the result of a poor coordination of orofacial, palatolingual, and head-neck muscles, and is probably also related to dystonic muscle activity. It is an important component of the burden of care for a patient's caregivers and a cause of impaired self-image for the child [9,15]. The improvements with trihexyphenidyl reported in this study also occurred with the use of other anticholinergics in other studies [16,17]. Although the supposed mechanism may involve the peripheral side effects of the medication, it may also result from a central action producing an increase in motor control of the muscles involved in swallowing. The latter mechanism could explain the improvement reported in expressive language here and in other studies [5].

A prospective, double-blinded, placebo-controlled trial with long term follow-up is needed to assess the efficacy of trihexyphenidyl for the treatment of dystonia and sialorrhea in children with cerebral palsy. The development and validation of more sensitive and specific dystonia severity rating scales for young children is imperative for the objective judgment of outcomes.

In conclusion, trihexyphenidyl is well tolerated and appears to be beneficial in the treatment of dystonia and sialorrhea in children with cerebral palsy. Trihexyphenidyl should be initiated at a low dose and gradually increased in a slow stepwise manner over several weeks, to promote tolerability and to allow for an often delayed beneficial response.

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