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Trihexyphenidyl for the Management of Dystonia in Children

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Trihexyphenidyl was approved by the Food and Drug Administration (FDA) on May 13, 1949 under the brand name Artane®.[1] Although indicated only for use in adults with Parkinsonism or for the control of extrapyramidal disorders caused by central nervous system drugs such as phenothiazines and thioxanthenes, it has become a common treatment for a wide variety of movement disorders.[1,2] For more than 20 years, it has been used in the treatment of dystonia in children with cerebral palsy.[4-11] In these patients, trihexyphenidyl may not only produce improvements in muscle tone, but also control of sialorrhea. This issue of *Pediatric Pharmacotherapy* will provide an overview of the pharmacology of trihexyphenidyl and describe the results of several recent studies of its use in children.

Mechanism of Action

It is believed that dystonia results from dysfunction in the basal ganglia. Overactivity of the indirect pathway of neurotransmission within the basal ganglia may be related to imbalance between dopaminergic and cholinergic systems. Trihexyphenidyl, a synthetic anticholinergic, acts as a competitive antagonist at muscarinic receptors to decrease acetylcholine. It may also improve dystonia through a direct relaxant effect on smooth muscle.[1-3]

Pharmacokinetics and Pharmacodynamics

Like other anticholinergics, trihexyphenidyl is rapidly absorbed after oral administration.[12,13] In a study of 8 adults being treated with doses of 2-8 mg/day, the average peak serum concentration was 7.15 $\pm$ 2.58 ng/mL, reached at an average of 1.32 $\pm$ 0.58 hours after a dose.[12] Trihexyphenidyl is metabolized in the liver via hydroxylation. The estimated elimination half-life in adults has been estimated at 5 to 10 hours, but newer studies have reported much longer values of up to 33 hours. The average onset of effect of trihexyphenidyl is seen within one hour after an oral dose in adults.[1,2] Peak effects typically occur within 2-3 hours, and the duration of effect ranges from 6 to 12 hours. The pharmacokinetic and pharmacodynamic characteristics of trihexyphenidyl have not been evaluated in children.

Clinical Trials

Despite the long history of trihexyphenidyl use in children with dystonia, there have been few clinical trials evaluating its efficacy. Studies from the 1980s documented a response rate of approximately 30-50% in children treated with high-dose therapy.[4,5] More recent studies have continued to produce mixed results. In 2001, Hoon and colleagues published a retrospective study of 22 children with cerebral palsy given trihexyphenidyl. The mean age of the patients was 4 years 10 months (range 1-12 years). The average dose was 0.13 mg/kg/day (range 0.04-0.3 mg/kg/day). At the time of data collection, the average duration of treatment was 9 months. Functional changes were rated by parents using a 5-point rating scale. Eight children (36%) had improvements rated at 4 or 5 for upper extremity function. Eight children had similar benefit in verbal expressive language, and 5 had a reduction in sialorrhea. None of the children had improvements in lower extremity tone. Adverse effects were generally mild. Two children discontinued therapy: one for constipation and one for irritability.

In 2007, Sanger and members of the Child Motor Study Group conducted a multicenter prospective, open-label, pilot trial of high-dose trihexyphenidyl in children with cerebral palsy with secondary dystonia.[7] Twenty-six children between 4 and 15 years of age were enrolled in the 15-week trial. All had dystonia impairing function of their dominant arm. Trihexyphenidyl was initiated at a dose of 0.05 mg/kg twice daily. At week 2, the dose was increased to 0.05 mg/kg three times daily. At weekly intervals, the dose was increased to a maximum of 0.25 mg/kg three times daily (0.75 mg/kg/day). This dose was

continued for 4 weeks, followed by a 5 week taper ending at week 15. The patients were evaluated at weeks 9 and 15.

Three patients withdrew due to adverse effects (chorea, rash, and hyperactivity). All adverse effects resolved after discontinuation. The 23 children who completed the study showed significant improvement in upper limb function at week 15 (p=0.45), but not at week 9. Three others required a dose reduction due to adverse effects. Post hoc analysis of the 10 children with hyperkinetic dystonia revealed worsening function at week 9, with a return to their baseline by week 15. Based on their results, the authors suggest that trihexyphenidyl may improve dystonia in children with cerebral palsy, but that beneficial effects may not been seen for several months after the start of treatment and may not occur in children with hyperkinetic dystonia.

In 2009, Rice and Waugh conducted a randomized, double-blind, placebo-controlled trial of trihexyphenidyl for dystonia in 16 children (ages 2-18 years) with cerebral palsy.[8] Patients were randomized to receive either trihexyphenidyl at an initial dose of 0.2 mg/kg/day with weekly titration up to 2.5 mg/kg/day or placebo three times daily. Response was assessed at week 12 (the end of the dose titration period) and week 28. Fourteen children completed the study.

At both assessment periods, the authors found no significant difference between the groups using the Barry-Albright Dystonia scores or the Quality of Upper Extremity Skills Test scores. There were significant treatment effects measured by the Goal Attainment Scale and the performance portion of the Canadian Occupational Performance Measure. All of the children receiving trihexyphenidyl experienced an adverse effect, including agitation, poor sleep, hallucinations, dry mouth, urinary incontinence, or constipation. Adverse effects were reported in 38% of the placebo controls. While trihexyphenidyl did not produce significant overall changes in their subjects' dystonia, the authors noted that there may be a place for this agent in helping children to achieve their individual goals. They recommend that future studies utilize more selective scoring tools to evaluate the efficacy of treatment.

In March 2011, Carranza-del Rio and colleagues conducted a retrospective study of their experience in 101 children with cerebral palsy treated with trihexyphenidyl for dystonia and/or sialorrhea.[9] The mean age of the patients at the start of therapy was 7 years 10 months (range 1-18 years). The average starting dose was 0.095 mg/kg/day (range 0.01-0.4 mg/kg/day) divided and given in two doses. Doses were increased by 10-20% at intervals of at least 2 weeks until benefit was seen or adverse effects made the drug intolerable. The average final dose was 0.55 mg/kg/day (range 0.03-3 mg/kg/day), with divided doses typically given twice or three times daily. The mean duration of therapy was 3 years and 7 months. Approximately one-third of the children (37.6%) were taking other antispasmodics and 38.6% had previously received botulinum toxin A injections.

A total of 97 patients experienced benefit, including reduced dystonia in an upper extremity (59.4%) or lower extremity (37.6%). Sixty percent had a reduction in drooling and 24.7% had improvement in their speech. Adverse effects were reported in 69% of the children, but 64% continued on therapy. The most frequently reported adverse effect was constipation, in 42.6% of patients. Most adverse effects resolved with dose reduction. Based on their findings, the authors concluded that trihexyphenidyl was generally well tolerated and effective in the majority of children treated.[9]

Ben-Pazi recently published an additional retrospective study in the *Journal of Child Neurology*.[10] He evaluated 31 children (mean age 8.2 $\pm$ 5.8 years) with dystonia who had been treated with the high-dose trihexyphenidyl regimen utilized in the Sanger study.[7] The mean maximum dose used in these patients was 0.72 $\pm$ 0.06 mg/kg/day). The majority of caregivers for the study patients (68%) reported improvement in dystonia for at least one body area. The greatest degree of improvement was seen in arm function, followed by hand function, oromotor function, leg function, and head/neck tone. Improvement was significantly greater in those children without spasticity and in those with higher cognitive function. Caregivers for 10 of the children also reported a reduction in tone and half noted an overall functional improvement. Adverse effects were reported in 19 children, but were typically mild. The most common adverse effect was transient irritability, reported in 13 children (37%).

In addition to its use in dystonia associated with cerebral palsy, trihexyphenidyl has been found to be of benefit in treating dystonic movements in girls with Rett syndrome. In 2010, Gika and colleagues described two girls, ages 9 and 13 years, who had experienced repeated acute life-threatening episodes (ALTEs) throughout childhood considered to be related to seizures.[13] These events began with arm extension and stiffening, followed by staring, apnea, bradycardia, and eventually cyanosis. After seizures were ruled out, a dystonic movement disorder was suspected. Both patients

experienced complete resolution of ALTEs after starting trihexyphenidyl.

Contraindications and Precautions

Trihexyphenidyl should not be used in patients with narrow-angle glaucoma, obstructive diseases of the gastrointestinal or genitourinary tracts, myasthenia gravis, achalasia, or a known hypersensitivity to the drug. It should be used with caution in patients with hyperthyroidism, renal or hepatic dysfunction, cardiac arrhythmias, peptic ulcers, esophageal reflux, or in children under 3 years of age.[1,2]

Adverse Effects

Up to 30 to 50% of patients taking trihexyphenidyl experience some degree of anticholinergic adverse effects, including dry mouth, blurred vision, tachycardia, pupillary dilation, headache, weakness, dizziness, headache, nausea, urinary hesitancy or retention, or constipation. Most patients tolerate these effects without the need for discontinuation. Some of these reactions will become less pronounced over time and may resolve without intervention. A small number of cases of suppurative parotitis, skin rash, paralytic ileus, delusions, or hallucinations have been reported with trihexyphenidyl use.[1,2]

Drug Interactions

Trihexyphenidyl produces additive adverse effects when given with other anticholinergics, including atropine. It may increase the effects of botulinum toxin or potassium chloride. It will decrease the effects of central acetylcholinesterase inhibitors and secretin.[1,2]

Earlier this year, De Rinaldis and colleagues described an interaction between sodium valproate and trihexyphenidyl in a 3-year-old girl with dystonic cerebral palsy and epilepsy.[14] The patient had severe hypoxic-ischemic injury at birth. She had been treated with sodium valproate 30 mg/kg/day and levetiracetam 40 mg/kg/day since 8 months of age with good seizure control. Trihexyphenidyl (0.5 mg once daily) was added at 33 months of age to reduce her generalized dystonia. The dose was gradually increased to 1 mg twice daily (0.16 mg/kg/day).

After 3 months, her seizures increased. A serum valproate level taken at that time was 40 mcg/mL, below the therapeutic range. The dose was increased to 45 mg/kg/day, but the level remained low. The authors theorized that the reduction in gastrointestinal motility may have impaired the absorption of sodium valproate, resulting in suboptimal serum concentrations. Discontinuation of the trihexyphenidyl following gradual dose reduction corresponded with an increase in the serum valproate level to 74 mcg/mL without an increase in the dose. Additional study in a controlled setting is needed further explore this potential drug interaction.[14]

Availability and Dosing Recommendations

Trihexyphenidyl is available from several manufacturers in 2 and 5 mg tablet strengths, as well as a 0.4 mg/mL lime-peppermint flavored oral elixir. The elixir contains 5% alcohol. Trihexyphenidyl may be given with or without food, but it is often better tolerated if taken with a meal.[1,2]

The recommended starting dose for trihexyphenidyl in adults is 1 mg. The dose may be increased by 2 mg increments every 3 to 5 days until the optimal response is achieved. In adults, doses are usually titrated to 6 to 15 mg. There is no established maximum dose.[1,2] Based on current studies, children with dystonia associated with cerebral palsy should begin therapy at 0.02-0.06 mg/kg given two or three times daily (up to a dose of 1-2 mg), with weekly increases of 0.05-0.1 mg/kg increments. Although, as in adults, no maximum dose has been established for children, a maximum daily dose of 2.5 mg/kg/day has been used in the more recent trials.[4-8]

Summary

Trihexyphenidyl provides a useful alternative or adjuvant to benzodiazepines, baclofen, dantrolene, or tizanidine in the management of dystonia in children. Clinical trials in children with dystonia associated with cerebral palsy have shown mixed results, with efficacy often demonstrated only after prolonged use. Trihexyphenidyl is not associated with significant toxicities at normal treatment doses, but many patients experience typical anticholinergic adverse effects, such as dry mouth and constipation, early in treatment. While not universally effective, a trial of trihexyphenidyl is warranted in any child with dystonia refractory to other antispasmodics.

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Pharmacology Literature Update

Adverse drug reaction monitoring

As background information for establishing a new screening program for drug safety, the authors of this study evaluated the pediatric case reports in the WHO global safety reporting database (VigiBase). Of the nearly 3.5 million reports from the years 1968 to 2010, 7% involved children. The largest differences in reporting between children and adults were noted with anti-infectives (33% of the pediatric reports versus 15% of the adult reports), respiratory drugs (11% versus 5%), and dermatologic agents (12% versus 7%). Thirty-five percent of all adverse reactions reported in children involved the skin, compared to only 23% of reports in adults. Adverse reactions resulting from medication errors were greatest in infants (28 days-23 months). The most common reactions in older children (ages 2-11 years) resulted from medications for attention deficit/hyperactivity disorder. **Star K, et al. Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. Drug Safety 2011;34:415-28.**

Anidulafungin kinetics in infants

While caspofungin is currently the only echinocandin antifungal approved by the FDA for use in the pediatric population, both micafungin and anidulafungin have been the focus of several new studies in infants and children. In the paper, the authors evaluated the pharmacokinetics of IV anidulafungin (1.5 mg/kg/day) in 15 infants. Mean area under the concentration-time curve (AUC) was similar between the groups (75 mcg h/mL and 98 mcg h/mL, p = 0.12). These values are also similar to values previously reported in children and adults using standard doses (AUC approximately 100 mcg h/mL). The authors suggest this similarity in values reflects the metabolic profile of the drug, nonenzymatic degradation in the blood, which is not influenced by age and growth-related changes in function. **Cohen-Wolkowiez M, et al. Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. Clin Pharmacol Ther 2011;89:703-7.**

Vancomycin dosing guidelines

The authors of this retrospective study evaluated vancomycin dosing strategies in 295 children admitted to their institution over a 5 year period. During the final year of the study, the recommended vancomycin dose had been increased from 40-50 mg/kg/day to 60 mg/kg/day based on concerns for microbial resistance. During the 2005-2008 period when the traditional target trough serum vancomycin concentration of 5-15 mcg/mL was in use, 78% of the dosing regimens met the goal. The target trough concentration of 10-20 mcg/mL during the final two years of the study, raised to coincide with the dose increase, was achieved in only 49% of cases. The authors suggest that higher doses of vancomycin (70-85 mg/kg/day) would be needed to achieve the new target trough concentrations in infants and children. **Eiland LS, et al. Assessment of vancomycin dosing and subsequent serum concentrations in pediatric patients. Ann Pharmacother 2011;45:582-9.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/27/11:

1. Micafungin (Mycamine™) was added to the Formulary as the sole echinocandin. It replaces both anidulafungin and caspofungin.
2. Diazepam rectal gel (generic) was added to the Formulary.
3. Ceftazidime was removed from the Formulary.
4. The restriction on ticarcillin/clavulanate (Timentin®) was amended to include combination therapy for Stenotrophomonas infections.

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