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Efficacy and Safety of Trospium Chloride Use in Children With Idiopathic and Neurogenic Detrusor Overactivity: An Overview of Available Data

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ABSTRACT

INTRODUCTION: There are limited data regarding treatment of idiopathic and neurogenic detrusor overactivity with anticholinergic drugs in children. Although oxybutynin and propiverine are authorized for use with children, treatment of this subgroup of patients is not officially approved for the newer anticholinergic drugs that have some advantages in tolerability. In particular, the quaternary drug trospium chloride (TC) has the benefit of not passing the blood-brain barrier (in contrast to the other anticholinergics, which are tertiary amines). The purpose of this article is to evaluate published data regarding the efficacy, safety, and dosage of TC in pediatric patients.

METHODS: Major computerized database indexes were analyzed for studies between 1960-2010 that involved treatment of children with TC and other anticholinergics. Key words used for searching were: *trospium chloride, anticholinergic, oral application, incontinence, urgency, pollakiuria*, and *children*. Variables compared across studies were the age of the patients, daily dose, duration of treatment, efficacy parameters, and safety aspects.

RESULTS: One randomized controlled trial with 58 participants and 3 uncontrolled studies with various inclusion criteria were identified in the literature. TC has been investigated in children aged between 3 and 14 years for a number of indications including bladder instability, neurogenic bladder dysfunction, and nocturnal enuresis. The reported studies ranged in length from 5 days to 12 weeks. In all studies, results showed improvement in symptoms for the majority of the patients. The occurrence of side-effects was low and none of the side-effects was severe.

CONCLUSIONS: A definite recommendation for the use of TC in children cannot be given due to insufficient data. Preliminary results indicate that its use may have potential advantages in children, but additional studies are needed.

KEYWORDS: Trospium chloride; Children; Incontinence; Anticholinergic; Dosage

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Abbreviations and Acronyms

TC, trospium chloride

INTRODUCTION

Anticholinergic medication and strict behavioral modification are the cornerstones of treating functional voiding disorders and incontinence in children [1]. Oxybutynin, propiverine, tolterodine, fesoterodine, and trospium chloride are anticholinergics that are frequently used for the treatment of incontinence. Although oxybutnin and propiverine are authorized for use with children (according to age and weight), the newer substances in the same group are not yet approved for the pediatric population. Anticholinergic medications such as oxybutynin are effective, but the high incidence of systemic

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side effects limits their use [2]. Therefore, evaluating other possible treatment options with better tolerability and equal effectiveness should be of high priority.

The efficacy of trospium chloride (TC) has been well described in many urodynamically controlled studies in adults with detrusor overactivity of neurogenic and idiopathic origin. Clinical trials with adult patients treated with TC have shown that it has a similar therapeutic outcome to oxybutynin with fewer adverse effects [3-5]. However, little has been published regarding use of TC in children, although its favorable side-effect profile and the fact that it does not cross the blood-brain barrier would suggest that it may be useful with this population [6,7]. The syndrome of childhood urinary incontinence, whose symptoms are imperative and frequent urinary urgency with wetting during the day and night, is distinct from the term "enuresis" (which usually means only nocturnal enuresis). In the past, treatment for childhood wetting did not distinguish between urinary incontinence and enuresis.

Although 80% of children with a dysfunction of the bladder have enuresis, the remaining 20% have urinary incontinence with differing underlying pathophysiology [8]. During childhood, this is most frequently due to detrusor overactivity. In addition to the nightly bed-wetting, daytime symptoms include imperative urinary urgency, pollakiuria, small micturition volume, and retaining maneuvers. Even though TC is widely used to treat adults with overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency, it is still contraindicated in children under 12 years of age. The purpose of this article is to evaluate published data regarding the efficacy, safety, and dosage of TC in pediatric patients.

METHODS

Computerized database indexes such as Medline (U.S. National Library of Medicine; Bethesda, MD, USA), BIOSIS (Thomson Reuters; NY, NY, USA), and Embase (Elsevier BV; Amsterdam, Netherlands) were analyzed for data from clinical studies published between 1960 and 2010 that involved treatment of children with TC and other anticholinergics. Key words used for searching were: *trospium chloride, anticholinergic, oral application, incontinence, urgency, pollakiuria,* and *children*. The variables compared across studies were the age of the patients, daily dose, duration of treatment, efficacy parameters, and safety aspects.

RESULTS

The database search revealed 1 randomized control trial [2] involving the use of TC in children and 3 studies without a control group [6,9,10]. Children involved in the investigations had an age range of 3-14 years and presented a variety of symptoms including irritable bladder, bladder instability, neurogenic bladder dysfunction, and nocturnal enuresis.

Clinical trial from 2003. Lopez Pereira et al [2] conducted the only multicenter, single-blind, randomized control trial in which the efficacy and most appropriate dosage of TC for managing bladder instability in children was assessed as compared with placebo. The 58 children enrolled in the study were aged between 5 and 13 years old and had urodynamically proven detrusor instability with symptoms of urinary urgency and daytime or nighttime wetting. The patients were randomly allocated to 1 of 5 groups based on TC dosage: 10, 15, 20, or 25 mg TC, or a placebo. The total daily dosage was split into 2 doses and administered daily for 21 days. The patient's symptoms, results of a voiding diary, and urodynamic values were collected at the beginning and end of the treatment period. Urodynamic parameters used to assess TC therapeutic efficacy were: number of uninhibited contractions, mean pressure of these contractions, and volume at first contraction. All adverse events were recorded at the final visit. Of 50 patients treated with TC, 82% had a positive therapeutic result versus 37.5% of patients with improvement in the placebo group. Therapeutic efficacy was classified into 1 of 4 categories: excellent, good, fair, or poor. An excellent result consisted of complete resolution of incontinence and > 30% improvement in at least 1 of the 3 urodynamic parameters evaluated (noted above); a poor result consisted of a decrease in incontinence episodes of < 50%. A significant improvement in the urodynamic parameters noted above was seen in 74% of patients. The most relevant urodynamic improvement was the number of uninhibited contractions. All patients had improvement of 30% in 1 or more of the analyzed urodynamic criteria. There were no statistically significant differences in therapeutic efficacy between TC doses, which is to be expected due to the small number of participants in each group. However, there was a significant difference when the treated group as a whole was compared with the placebo group. Ten percent of patients experienced minor side-effects that could be related to the medication. The criteria for evaluating the urodynamic efficacy of the drug might not be the most appropriate from a present-day point of view because it is still not known which urodynamic parameters best correlate with a satisfactory clinical response. However, the parameters used in the study were those that the authors considered to be most clinically important in children.

Uncontrolled study from 1991. Kiesswetter [10] conducted an open pilot study on the use of TC in 10 children with primary enuresis. Children with primary enuresis and a frequency of wetting of at least 50% were included in the treatment group.

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The duration of treatment was 84 days (12 weeks). The TC dose was adjusted according to body weight: 10 mg-0-10 mg TC was used for 25-30 kg body weight; 10 mg-0-20 mg TC was used for 20-40 kg body weight; 20 mg-0-20 mg TC was used for body weights over 40 kg. TC was administered daily at 8 am and 4 pm. In the observation period of 21 days before start of treatment, the children had 148 wetting episodes. During the treatment period between 21-42 days, the number of these episodes was reduced to 117; during the treatment period between 63-84 days (up to 12 weeks), there were 81 recorded episodes. After a 3-month treatment period, 3 patients were cured, 5 showed improvement, and 2 showed no improvement. No side-effects were reported. The results corresponded to a success rate of 80%, although one must bear in mind the small number of children involved in this study.

Uncontrolled study from 1998. Wiedemann et al [6] reported 2 identical noninterventional trials concerning use of TC in children from 292 and 800 general doctors' practices. The children had urinary incontinence and irritable bladder symptoms (including frequency and urgency). Pretreatment included psychopharmaceuticals, antibiotics, and other anticholinergics. Over a period of 4 weeks, 89 children aged less than 15 years with urinary incontinence and irritable bladder were treated with TC. Half of the patients were girls and half were boys. On days 7 and 28, data were collected regarding the subjective symptoms and tolerance to the medication using a documentation form. The most predominant symptom was urinary incontinence (89.9%); 19 children (21.4%) had imperative urinary urgency, and 66 children (74.2%) had pollakiuria. A total of 62.9% of the treated children received twice-daily 20 mg TC, 27% received once daily 20 mg, and 10.1 % received more than 40 mg TC. In older children who weighed more than 40 kg, 40 mg was used. A total of 79 of the 89 children received the planned dose of TC during the observation period; a dose adjustment occurred in 5 children. In 8 children, treatment was discontinued for a number of reasons and these patients were not included in the data evaluation. Results showed that the effect of TC was noted in 90.6% of cases within 7 days. In 46.3% of children, the symptoms or urinary incontinence were eradicated under TC. In the remaining children, a marked reduction in incontinence episodes was reported. After a 4-week treatment period, the symptoms of imperative urinary urgency were alleviated in 68.4% of the patients. In 35.3% of patients, pollakiuria subsided during treatment. In the remaining children, micturition frequency was reduced by 2.3 micturitions. Undesirable side-effects of dry mouth, reddening of the skin, and palpitations were documented in 3 children (3.4%). In over 94% of the patients, the tolerance to TC was assessed as "good" to "very good". Only 1 of the 8 children who did not continue therapy discontinued because of a drug-related side-effect (nausea). Some drawbacks of this study may be the short treatment period, small patient group, and subpopulation analysis.

Uncontrolled study from 2001. Danilov and Danilova [9] assessed the efficacy of administration of TC in children with neurogenic bladder dysfunction involving a variety of symptoms including pollakiuria, imperative urge to void urine, imperative incontinence, nocturnal incontinence, and leucocyturia. A group of 14 patients (age not specified by the authors) were enrolled in this observational study. All patients received 15-45 mg TC per day dependent on age (1-3 tablets of 5 mg, administered 3 times per day). The total duration of the therapy was 5 days. Following therapy, the urge to void urine was normalized in 12 patients; nocturnal incontinence disappeared in 4 patients and its frequency decreased in the 6 remaining patients. Pollakiuria disappeared in 4 patients and was less pronounced in 6 patients. Retrograde cystometry (a method whereby the bladder is filled by gravity in a retrograde fashion with the patient standing [11]) conducted before and after treatment showed significant urodynamic changes in terms of increased bladder capacity and reduction in number of micturitions, despite the short duration of treatment. The therapy was also well-tolerated and free of marked side-effects. The short duration of this open study and the very small patient group must be taken into consideration when interpreting the results.

DISCUSSION

Use of anticholinergics in children is not novel [12,13] and a few studies involving tolterodine, propiverine, or oxybutynin can be found in the literature [14-16], although some of the results have been questioned [17-19]. However, the number of studies involving use of TC in children is limited. TC has been investigated in children aged between 3 and 14 years for a number of indications including bladder instability, neurogenic bladder dysfunction, and nocturnal enuresis. The reported studies ranged in length from 5 days to 12 weeks. In all studies, results showed improvement in symptoms for the majority of the patients. The occurrence of side-effects was low and none of the side-effects was severe.

Table 1 contains a summary of the studies involving use of TC with children. The studies presented in the table provide preliminary evidence that successful treatment of children with TC seems to be possible. Use of oral TC preparations (eg, Spasmex; Dr. Pfleger GmbH, Bamberg, Germany) provides the possibility of flexible, individual dosage schemes that allow either a reduction or increase in dose according to treatment success and tolerability to the medication. An appropriate

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Table 1. Summary of the Primary Studies Using Trospium Chloride (TC) to Treat Children With Idiopathic and Neurogenic Detrusor Overactivity.

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Authors [Reference]	Number Treated With TC	Age (years)	Indication	Study Length (days)	Total Daily Dosage	Symptom Improvement (% n)	Side Effects (All Minor) (% n)
Lopez Pereia et al [2]	50	5-13	bladder instability	21	10, 15, 20 or 25 mg	82% overall	10%
Kiesswetter [10]	10	not specified	primary enuresis	84	20-40 mg according to body weight	80% overall	0
Wiedemann et al [6]	81	3-14	urinary incontinence; irritable bladdder	28	20-40+ mg according to body weight	100% incontinence 68.4% urgency 35.3% pollakiuria	3.4%
Danilov and Danilova [9]	14	not specified	neurogenic bladder dysfunction	5	5-45 mg	85.7% urge to void 71% nocturnal incontinence 71% pollakiuria	0

pediatric dosage must take into account the age and weight of the child and the severity and nature of the symptoms. In the described studies, TC was often given according to the weight of the child, with those over 40 kg receiving the normal adult dose. It is interesting to note that there was no significant correlation between TC dose and adverse secondary effects in the clinical trial [2]. A review of the treatment success at regular intervals is of critical importance to allow for dose adjustment, if necessary. In the case of a complete cure, discontinuation of therapy may also be considered.

The encouraging nature of the preliminary results from the presented studies, along with the positive side-effect profile and lack of central nervous system effects, make TC an attractive option to consider. However, the studies to date have a small number of patients with different inclusion criteria and there has only been 1 clinical trial with 58 participants. Therefore, a definite recommendation for the use of TC in children cannot be given due to insufficient data. Additional studies are needed before TC can be considered for standard use in children with symptoms of ideopathic and neurogenic detrusor overactivity.

Conflict of Interest: none declared.

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