

Behavioral Effects of Long-Term Antimuscarinic Use in Patients with Spinal Dysraphism: A Case Control Study

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Abbreviations and Acronyms

CBCL = Child Behavior Checklist
CNS = central nervous system
SD = spinal dysraphism

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Purpose: We explored possible associations between long-term antimuscarinic use and behavioral problems in children with spinal dysraphism and neurogenic bladder.

Materials and Methods: Children with open and closed spinal dysraphism were recruited from 2 pediatric hospitals, 1 in Amsterdam and 1 in Utrecht, The Netherlands. At the Amsterdam facility antimuscarinics were prescribed in selected patients with detrusor overactivity. At the Utrecht facility antimuscarinics were prescribed from birth onward in patients with spinal dysraphism beginning in the early 1990s. Parents of study participants were asked to fill out a Child Behavior Checklist. Demographics, data on level and type(s) of lesion, and presence of hydrocephalus with a drain (and, if applicable, number of drain revisions) were retrieved for each patient. Cases and controls (8 boys and 8 girls per group) were matched on a 1-to-1 basis.

Results: Data on 32 children were analyzed. Median age was 10.6 years in cases and 10.5 years in controls ($p = 0.877$). In each group 9 of 16 patients had hydrocephalus with a drain. No significant difference in Child Behavior Checklist scores for total problems was found between cases and controls (median 52.0 vs 59.5, $p = 0.39$). No differences were found between the groups on any subdomain of the Child Behavior Checklist.

Conclusions: No significant differences in behavior were found between children with spinal dysraphism with and without long-term use of antimuscarinics.

Key Words: antimuscarinic antagonists; behavior; meningomyelocele; spinal dysraphism; urinary bladder, neurogenic

NEUROPATHIC lower urinary tract dysfunction in patients with spinal dysraphism has been treated since the late 1980s with a proactive regimen of early clean intermittent catheterization and antimuscarinic drugs from birth onward. In pediatric cohorts this approach has proved to be effective and to preserve function of the lower and upper urinary

tract.¹⁻³ Children with neuropathic detrusor overactivity and a good therapeutic effect of antimuscarinics are by current standards considered to have a lifelong dependence on antimuscarinic treatment.⁴ In the Netherlands oxybutynin is the most commonly prescribed antimuscarinic drug for children with dysraphism and the only antimuscarinic drug

that is currently accepted for pediatric use. Oxybutynin acts by blocking efferent parasympathetic M3 receptors innervating the detrusor muscle, thus inhibiting bladder contraction. However, oxybutynin is not M3 receptor specific and also affects other subtypes of muscarinic receptors, such as the M1 and M2 receptors. This action results in side effects such as dry mouth (which is observed frequently and may lead to dental problems) and constipation.⁵ Apart from effects on the autonomic nervous system, oxybutynin also works through blockage of calcium channels.

Due to its high lipophilicity, neutral charge and relatively small molecular structure, oxybutynin easily crosses the blood-brain barrier.⁶ Oxybutynin has been shown to induce electroencephalographic changes in healthy volunteers.⁷ All subtypes of muscarinic receptors (M1, M2, M3, M4, M5) are present in the brain. Especially M1 receptors are thought to be of importance for cognitive function, being abundantly present in the neocortex, hippocampus and neostriatum.⁸ Because of the action on M1 receptors, cognitive dysfunction is a known side effect of oxybutynin. Anxiety, somnolence and hallucinations are the other negative CNS side effects observed in some patients.

At several institutions where children with SD are treated the early use of antimuscarinic drugs is avoided because of fear of changes in the functioning of the developing brain. As an alternative to clean intermittent catheterization and antimuscarinics, incontinent vesicostomy is used to guarantee unobstructed bladder outflow. However, no study has investigated whether long-term use of antimuscarinic medication can lead to structural impairment of mental functioning. CNS side effects might lead to various problems (including deviant behavior) compared to patients with SD not using oxybutynin. To our knowledge this hypothesis has not previously been tested. We studied the possible behavioral effects of long-term use of oxybutynin from birth onward in children with SD.

PATIENTS AND METHODS

Permission from the ethical review board was obtained. Two institutions took part in this study, both of which have multidisciplinary teams for children with SD. These children are seen on a regular basis, depending on age and clinical course, but at least once yearly. At the pediatric hospital in Amsterdam antimuscarinic treatment has been used only on indication but has not been standard treatment in all children from birth onward, whereas at the pediatric hospital in Utrecht all children with SD received antimuscarinics from birth onward.

The control group (recruited primarily in Amsterdam, with 65 children with SD presenting from June 2012) had a diagnosis of open or closed SD (ICD10 Q05 and Q76).

Included were children 6 to 18 years old who either had never used antimuscarinic medication or had only used it for a brief period (1 month or less). Baseline characteristics (type of SD), neurological level of the lesion (defined as the most caudal neurologically intact level, determined by physical examination), presence of hydrocephalus, presence and type of CNS drain, and number of drain revisions were noted. Excluded were children 6 years or younger and those with severe mental retardation (not able to attend any school, severely impaired communicative skills).

The case group consisted of patients who had used oxybutynin from birth onward. They were matched on a 1-to-1 basis by gender, age, type of lesion, presence of hydrocephalus and, if possible, by number of drain revisions. Patients used oxybutynin orally or intravesically. Both of these routes were included, since intravesical oxybutynin also enters the circulation and can cause systemic side effects. The case group was matched with the control group for practical reasons because controls were less readily available. The medication used in the case group was oxybutynin immediate release, most often prescribed orally (9 patients) at a dose of 0.3 mg/kg 3 times daily. Intravesical oxybutynin (4 patients) was given to those children who did not achieve sufficient urodynamic and clinical effect with oral oxybutynin or who were bothered by side effects. Tolterodine had been used for 15 years in 1 patient, and 1 patient had switched to solifenacin only a couple of months before completing the questionnaire.

All patients were invited to participate in the study by letter with informed consent form. A CBCL questionnaire for children 6 to 18 years, to be completed by the parents, was attached. CBCL is a 4-page validated questionnaire used to evaluate behavioral and emotional problems. The surveys were completed voluntarily, and there was no financial compensation for the participants.

For this study we used the "Problem" questions (120 multiple-choice questions) on the CBCL.⁹ This survey has been used to evaluate behavioral outcomes in children with SD but not to measure the effects of oxybutynin treatment.^{10,11} Outcomes are scored on the syndrome scales of anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule breaking behavior and aggressive behavior. Broader subcategory analysis results in scores on the internalizing, externalizing and total problems scales. Internalizing behavior is characterized by an inhibited style (eg by being anxious/depressed or withdrawn, or by developing psychosomatic complaints). Externalizing behavior refers to outward expression of emotions and acting out types of behavior (eg aggressive and delinquent behavior).

After 4 weeks all patients were contacted by telephone as a reminder to complete the questionnaire. In total 6 months were allowed to collect all CBCL questionnaires. All completed questionnaires were subsequently entered into a database using specially designed software (Assessment Data Manager, version 7.2, ASEBA®). T-scores were standardized based on Dutch test norms. Moreover, we assessed whether T-scores fell within the subclinical, clinical or borderline range (which is highly variable by

gender and age category). Normality of differences between the 2 groups was studied by plotting histograms that were compared using a Gaussian curve to examine the distribution. Because the differences were not normally divided, nonparametric tests were used.

The case group was compared to controls using SPSS®, version 20.0 for Windows. Wilcoxon matched-pair signed rank test was used in case of continuous variables, McNemar test (2 outcomes) or McNemar-Bowker test (more than 2 outcomes) was used in case of discrete variables, and $p < 0.05$ was considered statistically significant. These methods were chosen because the data were paired. The group using intravesical oxybutynin was compared to the group taking oral formulations using nonpaired testing (Fisher exact test in case of discrete variables and Mann-Whitney U test in case of continuous variables), and $p < 0.05$ was considered statistically significant.

RESULTS

Collection of Data

A total of 25 children were selected for the control group, of whom 17 (68.0%) returned completed and usable CBCLs. Unfortunately 1 child from the control group (a 17-year-old girl with closed SD) could not be matched with a child from the case group. The initially approached case group consisted of 35 children, from whom 26 usable responses were collected (74.3%). A total of 16 children were selected for 1-to-1 match. The CBCL was completed by the biological parent in 30 cases, an adult sibling in 1 and a nurse (who helped the child daily at home) in 1.

Baseline Results and Matching

Baseline characteristics are shown in the table. Each group consisted of 8 boys and 8 girls. Demographic matching was successful. Children in the case group were slightly (but not significantly) older than controls (10.6 vs 10.5 years, $p = 0.877$). Median age at which antimuscarinic treatment was started was 0.3 years (IQR 0.02–2.8), and median duration of antimuscarinic use was 8.3 years (7.0–13.3). No antimuscarinics were used in the control group.

Each group included 9 children with hydrocephalus (all with ventriculoperitoneal drain). It was impossible to match for all numbers of drain revisions. All 8 children without drain revisions could be matched to each other. However, 3 patients with more than 3 revisions were matched to children with 3 revisions, 2 revisions and 1 revision each. An exact match regarding type of lesion could not be achieved in 3 patients. In all 3 pairs patients with open SD had to be matched to patients with closed lesions, although none of these patients had hydrocephalus and all were neurologically intact.

Baseline characteristics of cases and controls

	Cases	Controls	p Value
Median yrs age (IQR)	10.5 (8.0–14.9)	10.6 (8.3–15.3)	0.877
No. gender/total No. (%):			
Male	8/16 (50.0)	8/16 (50.0)	1.000
Female	8/16 (50.0)	8/16 (50.0)	
No. hydrocephalus with drain/total No. (%)*	9/16 (56.3)	9/16 (56.3)	1.000
No. drain revisions/total No. (%):			
0	4/9 (44.4)	4/9 (44.4)	0.564
3 Or fewer	2/9 (22.2)	1/9 (11.1)	
More than 3	3/9 (33.3)	4/9 (44.4)	
No. open SD/total No. (%):	12/16 (75.0)	9/16 (56.3)	0.549†
Meningocele (neurologically intact)	1/16 (6.3)	0/16 (0.0)	
Myelomeningocele	11/16 (68.8)	9/16 (56.3)	
No. closed SD/total No. (%):	4/16 (25.0)	7/16 (43.8)	
Lipomyelomeningocele	1/16 (6.3)	2/16 (12.5)	
Split cord malformation	0/16 (0.0)	1/16 (6.3)	
Spinal lipoma	2/16 (12.5)	3/16 (18.8)	
Tethered cord	1/16 (6.3)	1/16 (6.3)	
No. neurological level/total No. (%):			
Intact	5/16 (31.3)	5/16 (31.3)	0.607
Sacral	1/16 (6.3)	0/15 (0.0)	
Lumbar	9/16 (56.3)	9/16 (56.3)	
Thoracic	1/16 (6.3)	2/16 (12.5)	

* All patients with hydrocephalus had a drain.

† Closed vs open SD distribution in cases and controls.

CBCL Outcomes

Continuous scores of the CBCL outcomes are listed in supplementary table 1 and categorical data are presented in supplementary table 2 (<http://jurology.com/>). There were no significant differences between the groups on any of the domains of the CBCL for continuous or discrete data. Median overall T-score was similar in both groups (52.0 vs 59.5, $p = 0.39$, median difference 4.0). The same applies to internalizing problems (53.3 vs 60.5, $p = 0.485$, median difference 3.5) and externalizing problems (47.5 vs 51.0, $p = 0.170$, median difference 7.5).

Although clinical behavioral problems occurred slightly more often in the control group (4 vs 2 children), this difference was not significant ($p = 0.172$). The differences between the 2 groups regarding occurrence of borderline and clinical internalizing and externalizing problems were also not significant ($p = 0.241$ and $p = 0.392$, respectively). A near significant greater number of children with withdrawn/depressed problems was seen in the control group (1 with clinical problems in case group vs 5 in control group, $p = 0.082$).

Overall patients using intravesical oxybutynin (4) did not have fewer behavioral problems compared to those using oral drug (1 of 4 vs 1 of 12, $p = 0.607$). This result also applies to internalizing and externalizing clinical problems (1 of 4 vs 1 of 12, $p = 0.245$, and 0 of 4 vs 1 of 12, $p = 0.450$, respectively). Also there was no significant difference in median scores of the CBCLs (51.0 for oral vs 54.5 for intravesical drug, $p = 0.361$).

DISCUSSION

The aim of this study was to examine possible effects of long-term antimuscarinic treatment on behavior in children with SD. According to parental ratings, there were no differences in behavior between patients who did and did not have a history of long-term use of antimuscarinics.

Oxybutynin is known to cause various CNS side effects. To overcome this problem, alternative routes of administration have been tried, including intravesical instillation (to overcome systemic effects) and adhesive plasters. Other antimuscarinics (which are claimed to be more M3 specific) have also been developed, including darifenacin, solifenacin and tolterodine. However, none of these agents is registered for pediatric use in The Netherlands. In the present study tolterodine was used by 1 child for a longer period (15 years) and solifenacin was taken by 1 patient for a short period.

Side effects of oxybutynin have mainly been studied in adult populations, and pediatric series have not included patients with SD using antimuscarinics for longer periods. No studies are available on behavioral problems in children with long-term use of antimuscarinics, and few series have investigated CNS side effects after oxybutynin use. A study by Ferrara et al revealed side effects with intravesical and orally administered oxybutynin in patients with SD.¹² In the oral group no CNS side effects occurred. In the intravesical group cognitive effects were observed, particularly attention deficits and difficulties with basic math operations. Two patients experienced drowsiness and 1 had hallucinations, which led to discontinuation of the drug.¹²

Giramonti et al evaluated 14 children taking antimuscarinics, of whom 1 had myelomeningocele.¹³ This small double-blind crossover trial showed that long-acting oxybutynin and tolterodine had no negative effects on attention or memory. However, the authors concluded that "other cognitive functions might be affected." A summary of post-marketing case reports in children identified hallucinations as the most frequently observed central antimuscarinic effect, followed by agitation, confusion, amnesia and abnormal dreams.¹⁴

Under powering may have biased the current study results. It is interesting that 2 near significant findings were observed (rule breaking behavior, $p = 0.06$, and withdrawn/depressed behavior, $p = 0.08$). A slightly larger sample size might have revealed significant findings, in which case there would have been fewer problems in the control group. These results could partly be explained by anticholinergic effects in the brain. To some extent, antidepressant and antipsychotic medications work

through their action on muscarinic receptors. Thus, antimuscarinics could hypothetically have a positive effect on behavioral aspects, although these possible effects should not be exaggerated based on our small series.

The present study has some limitations, including the small sample size. If the groups had been slightly larger, effects might have been found. A larger study in The Netherlands will be difficult to implement, although it might be possible in other countries. Because of the already small sample size, we also included a patient on tolterodine and 4 patients on intravesical oxybutynin. Theoretically these formulations have fewer side effects than orally administered oxybutynin and could lead to an underestimation of the behavioral effects.

This series does not focus specifically on cognitive outcomes, although some cognitive issues are addressed by the CBCL questions. Since our study was not designed to examine the effects on cognitive outcomes in children, a new trial should be done in which neuropsychological functioning is assessed. Ideally the study should be prospective, ie baseline IQ/CBCL scores should be known a priori. Lack of the latter is a shortcoming of this series. Only a prospective study could overcome these problems. However, the quickly decreasing size of the pediatric SD population in The Netherlands, along with the increasing number of children on antimuscarinics, will make such a study difficult to perform. Finally, because children with SD can suffer various types of behavioral problems, as shown in the present and earlier studies,¹⁵ our results may be biased. Although we attempted to achieve 1-to-1 matching with the aim of eliminating the risk of bias, some bias will inevitably be present.

CONCLUSIONS

In children with SD no differences in behavior could be demonstrated between those with long-term use of antimuscarinics and those never using these medications. It appears that patients with SD receiving long-term antimuscarinic treatment have no increased risk of cognitive dysfunction. These data may serve as additional support when discussing the safety of antimuscarinics, even when started at a young age.

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