Does Oxybutynin Hydrochloride Cause Arrhythmia in Children with Bladder Dysfunction?

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Aim: Pediatric surgeons frequently encounter children presenting with voiding dysfunction symptoms, including urgency, frequency, and incontinence. Antimuscarinic agents (Oxybutynin) are the main drugs used to treat patients with overactive bladder (OAB) syndrome, defined as urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia. Increased QT dispersion is known to be the cause of ventricular arrhythmia in various systemic diseases and leads to increased mortality and morbidity. Method: This study represents a subset of a complete data set, considering only those children aged admitted to the Pediatric Surgery and Pediatric Nephrology Clinics during the period January 2011 to July 2012. Result: In this study, we have determined that the QT interval changes significantly depending on the use of oxybutynin. The QT changes increased cardiac arrhythmia in children. Conclusion: For this reason, children using such drugs should be closely monitored for cardiac arrhythmia. Key words: cholinergic antagonists; oxybutynin; urinary incontinence; overactive bladder; children; QT interval.

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1. INTRODUCTION

Pediatric surgeons frequently encounter children presenting with voiding dysfunction symptoms, including urgency, frequency, and incontinence. This clinical occurrence often suggests overactive bladder and, thus, failed bladder filling. Antimuscarinic agents are the main drugs used to treat patients with overactive bladder (OAB) syndrome, defined as urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia (1). Anticholinergic agents such as oxybutynin chloride have been effective for overactive bladder (2). The treatment of OAB with antimuscarinics is not curative, and since OAB is a chronic disease, treatment may be lifelong. There is a concern that antimuscarinics used for the treatment of OAB can cause increases in HR that may be harmful. Another concern is whether or not these drugs have a potential risk of producing QT interval changes (3, 4). Antimuscarinic-induced increases in HR may put these patients at increased risk. However, increases in HR have, as a rule, not been reported as a major adverse effect in OAB studies of antimuscarinics, and use of these drugs did not seem to increase the risks of ventricular arrhythmias and sudden death in older patients, according to a retrospective database study (5).

Antimuscarinic drugs especially oxybutynin used for bladder dysfunction in children. Information about the cardiac side effects of these drugs in children is not available in the literature. Our goal in doing this work is to determine the effects on QT dispersion caused by the use of antimuscarinic drugs in children.

2. PATIENTS AND METHODS

This study represents a subset of a complete data set, considering only those children aged admitted to the Pediatric Surgery and Pediatric Nephrology Clinics during the period January 2012 to July 2011. Boys and girls aged 5–15 years were eligible for inclusion in the study if they had urinary urgency and frequency (8 micturitions on average per 24 h), and/or urge incontinence (incontinence episodes in the daytime at least once a week). Children presenting with overactive bladder, persistent incontinence, and a partial UDS response to an optimal dose of a well-tolerated, extended-release anticholinergic were invited to enter a prospective, open-label protocol. This study was approved by our institutional ethics board. A group of 3 female and 17 male patients was prospectively enrolled and followed a minimum of 1 month after beginning anticholinergic treatment. A total of 20 patients with nonneurogenic overactive bladder were included in this study using well-defined criteria, including intensive medical and behavioral therapy that failed to cure...
urgency and incontinence symptoms, absent correctable neurological anomalies. We observed these patients for QT dispersion, age, gender, heart rate, and body weight.

Before study inclusion, a complete questionnaire, physical examination, urinalysis, abdominal ultrasound, ECG, and echocardiograph were done. As part of the systematic follow-up, every month, patients were re-evaluated with a detailed questionnaire, physical examination, urinalysis, and ECG.

Patients were excluded if they had cardiovascular, hepatic, renal, gastrointestinal, or haematological disease, psychiatric disorder, or diabetes insipidus. Patients were also excluded if they had known anatomical abnormalities of the urinary tract, episodes of bacteriuria within 4 weeks before the study start, any condition that was a contra indication for anticholinergic therapy, treatment with other drugs having effects on the lower urinary tract, a residual urine volume (measured by ultrasonography) of >5 mL at repeated investigations (at the pre-trial screening), a history of clinically significant hypersensitivity or severe allergy, or a history of severe adverse drug reaction or intolerance to anticholinergic drugs.

Electrodes were inserted in anatomical positions according to routine procedure and ECG strips were recorded for 10 seconds with a standard device. 12-lead electrocardiograms (ECG) of all the patients were obtained at amplitude of 20mm/mV and a velocity of 50mm/s. The patients were subjected to manual ECG analysis by three cardiologists who were blinded to the study. QT intervals were manually measured in all possible leads. The QT interval was defined as the interval from the onset of the QRS complex to the end of the T wave, which was defined as its return to the T-P baseline. The measurements were carried out with a precision of 0.01 mm (0.4 ms). If the U wave was present, the QT interval was measured to the nadir of the curve between the T and U waves (6) (Figure 1).

The QT intervals were corrected using Bazett’s formula to compensate for its known dependence on heart rate: $QTc = QT / \sqrt{RR}$. Measurements of QT and RR intervals were carried out in 3 consecutive cardiac cycles in all leads, and average values were obtained [7]. QT dispersion was determined as the difference between the maximal and minimal corrected QT interval in different leads.

The mean ± standard deviation was observed. The paired t-test was used for repeated measurements. All statistical analyses involved SPSS for Windows version 15.0 (SPSS, Chicago, IL, USA); p values <0.05 were accepted as statistically significant.

3. RESULTS

The study included a total of 3 girls and 17 boys who had persistent urgency and incontinence after a minimum of 1 month of therapy with an optimal dose of a well-tolerated, extended-release oxybutynin hydrochloride treatment. The mean patient age was 9 years (range 5 to 15) (Table 1). There was a predominance of boy patients 17 (85%) among the admissions; girl patients accounted for 3 admissions, a rate of 15%. The age and body weight of the patients caused no statistically significant difference.

All electrocardiograms and urinary analyses were normal. No urinary upper tract deterioration was noted on subsequent ultrasounds. Tolerability was assessed by documenting agent therapy experience using a questionnaire administered by a pediatric surgeon. The patients and parents were asked to report any adverse event as soon as it occurred to prevent recollection bias.

A comparison of the QT wave variability parameters of both analyses demonstrated that there was a significant difference between the QT max and QT min values (p: 0.05); the QT wave dispersion levels of the patients were higher than in the initial analysis (p: 0.05) (Table 2). The heart rate before and after the administration of oxybutynin showed no statistically significant difference (Table 1).

4. DISCUSSION

Oxybutynin has historically been the drug of choice for the treatment of overactive bladder in adults; it has also been widely used in children. All anticholinergic drugs can have bothersome adverse effects. Dry mouth is the most common; however, constipation, gastro-oesophageal reflux, blurred vision, urinary retention, and adverse cognitive effects can also occur, although these symptoms are generally less bothersome in children (8). Oxybutynin appears to be particularly noxious in children, with reports of CNS effects such as hallucinations, psychosis, and concentration problems (9).

Jones et al. investigated the cardioactive properties of oxybutynin in guinea pigs and rabbit cardiac tissue.
Abrams et al. compared the efficacy, safety, and tolerability of oxybutynin and propiverine in a randomized cross-over study. HR and HRV were monitored with ECG recordings on a Holter monitor at baseline and at the end of the treatment period. The patients on regimen of propiverine 20 mg daily and propiverine 15 mg three times a day had a statistically significant increased HR and decreased HRV. Patients on oxybutynin had a similar HR and HRV compared with those on placebo (11).

QT prolongation is produced by many widely used drugs, such as the antiarrhythmic agents sotalol, amiodarone, quinolone, macrolide antibiotics, and methadone. A larger difference between the action potential duration in adjacent regions of the ventricular myocardium enables circular reentry activity between areas with delayed repolarisation and those with excitable myocytes (12). QT dispersion indicates ventricular repolarisation time and heterogeneity. Increased QT dispersion is known to be the cause of ventricular arrhythmia in various systemic diseases and leads to increased mortality and morbidity. (13).

Information on the possible QT effects of oxybutynin in patients is scarce, and specific studies seem to be lacking. The drug did not cause changes in the ECGs of elderly patients with urinary incontinence (14).

Among the more serious concerns related to the antimuscarinics used in the treatment of OAB are the risk of adverse cardiac effects, particularly increases in HR, QT interval prolongation, and the induction of polymorphic ventricular tachycardia (torsade de pointes). However, the potential of the different agents to increase HR or to prolong the QT interval has not been extensively explored (15).

The aforementioned studies were performed in adults. Cardiac side effects in adults have been revealed. There is no study addressing the cardiac side effects and the effects on the QT of the use of oxybutynin in children. In our study, we determined that the QT interval changes significantly depending on the use of oxybutynin. The QT changes increased cardiac arrhythmia in children. For this reason, children using such drugs should be closely monitored for cardiac arrhythmia.

REFERENCES


