SHORT COMMUNICATION

Use of propranolol in children with primary nocturnal enuresis

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ABSTRACT

In nocturnal enuresis, motivational therapy, alarm therapy, and drug therapy, such as anticholinergics, imipramine, and sertraline, are the mainstay of treatment. In the present study, we used motivational therapy, oxybutynin, and propranolol in children with primary nocturnal enuresis to determine if propranolol is an effective treatment. Fifty-two children with primary nocturnal enuresis were included in the study. Firstly, motivational therapy was given for 1 month to all patients. Patients who failed the motivational therapy were randomly given oxybutynin or propranolol. The patients were re-evaluated after 1 month of drug therapy. There was not a significant difference between oxybutynin and propranolol groups for initial frequency of nocturnal enuresis ($p > 0.05$). Of 52 patients, 28 (53.8%) patients improved by motivational therapy. There were 14 patients in the oxybutynin group. One patient was excluded from the study because facial flushing and mouth drying developed in the first week of oxybutynin therapy. In oxybutynin group, 12 of 13 (92.3%) patients improved. There were 10 patients in the propranolol group. In the propranolol group, while nine (90%) patients did not improve, one patient had significant remission (90%, $p < 0.001$). No significant adverse reaction was noted during propranolol therapy. There was no significant difference between oxybutynin and propranolol groups for initial frequency of nocturnal enuresis ($p > 0.05$). A significant difference was found between the groups for the remission of nocturnal enuresis ($p < 0.001$). Our findings showed that motivational therapy is the first line treatment in primary nocturnal enuresis, and oxybutynin but not propranolol is effective in patients who failed with the motivational therapy.

KEYWORDS

Primary nocturnal enuresis; Child; Motivational therapy; Oxybutynin; Propranolol.

INTRODUCTION

Enuresis is a common and possibly underestimated condition. It is termed as being "primary" if no continence has ever been achieved or "secondary" if it follows at least 6 months of dry nights. Its prevalence is above 10% among 6-year-old

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children, around 5% among 10-year-olds, and 0.5%–1% among teenagers and young adults [1,2]. Motivational therapy, alarm therapy, and drug therapy such as anticholinergics, imipramine, and sertraline are the mainstay of treatment [3].

We did examine a child with a migraine and primary nocturnal enuresis, whose enuresis incidentally improved after giving prophylactic propranolol therapy for her migraine attacks. In this study, we used motivational therapy, oxybutynin, and propranolol in children with primary nocturnal enuresis to test our above clinical observation in a large patient group, and to determine if propranolol is effective in the treatment of primary nocturnal enuresis.

METHODS

This study has been performed at Necmettin Erbakan University, Faculty of Medicine, Department of Pediatric Neurology, between January 2013 and August 2015. Inclusion criteria were as follows: Children, who were older than 5 years, without a period of six consecutive months of nighttime urinary control. Children with urinary incontinence initiated after 5 years of age or after a dry period about 6 months (secondary nocturnal enuresis); nocturnal enuresis caused by an organic pathology (for example, myelomeningocele, chronic renal failure, or diabetes mellitus); children who used a drug (for example, montelukast sodium or inhaler drug due to bronchial asthma); children with chronic disease such as pulmonary, hepatic, cardiac, and metabolic disorder; and children given a drug for nocturnal enuresis for the last 6 months were not included in the study.

Demographic data were obtained from the patients. A detailed physical examination, including heart rate, blood pressure, and cardiologic examination was performed in all patients. In order to detect etiological or other accompanying abnormalities; hematological, biochemical, and microbiological tests; urinary ultrasound, lumbosacral magnetic resonance imaging, and electrocardiography were performed in required patients.

Firstly, motivational therapy was given in all patients for 1 month as mentioned by Neveus et al. [4]. Patients with urinary incontinence less than twice a week after motivational therapy were accepted as "improved." Patients who failed motivational therapy were given oxybutynin or propranolol by using simple randomization and non-blinded trial. The patients were re-evaluated after 1 month of drug therapy. The study was approved by the Ethical Committee of Meram Medical Faculty. A written consent was received from the patients' parents.

RESULTS

Fifty-two children with primary nocturnal enuresis were included in the study. The mean age of patients was 7.83 ± 2.31 years. Thirty-one (59.6%) were males and 21 (10.4%) were females. Motivational therapy was provided for 52 patients. Of 52 patients, 28 (53.8%) improved by motivational therapy. The mean age of these patients who improved by motivational therapy was 7.71 ± 2.08 years and 19 (67%) were males and nine (33%) were females. Initial frequency of nocturnal enuresis was as follows: Every night in 18 patients and 3–6 per week in 10 patients. Improvement ratios by motivational therapy were as follows: 6 (21.5%) patients had complete remission (100%), 21 (75%) patients had significant remission (75%–100%), and one (3.5%) patient had 50% remission.

There were 14 patients in the oxybutynin group. One patient was excluded from the study because facial flushing and mouth drying developed in the first week of oxybutynin therapy. The mean age of the remaining 13 patients was 7.03 ± 1.93 years and nine (70%) were females and four were males (30%). Initial frequency of nocturnal enuresis was as follows: Every night in five, 3–6 per week in six, and 2 per week in two patients. In the oxybutynin group, 12 of 13 (92.3%) patients improved; three (25%) patients had complete remission (100%), five (41.7%) patients had significant remission (75%–100%), and four (33.3%) patients had (50%–75%) remission. Aside from one patient, we did not note any significant adverse reaction during oxybutynin therapy.

There were 10 patients in the propranolol group. The mean age of patients was 9.3 ± 2.79 years and eight (80%) were males and two (20%) were

females. Initial frequency of nocturnal enuresis was as follows: Every night in three, and 3–6 per week in seven patients. In the propranolol group, while nine (90%) patients did not improve, one patient had significant remission (90%). No significant adverse reaction was noted during propranolol therapy. There was no significant difference between oxybutynin and propranolol groups for initial frequency of nocturnal enuresis ($p > 0.05$). A significant difference was found between the groups for the remission of nocturnal enuresis ($p < 0.001$). Propranolol was not effective in improving nocturnal enuresis.

DISCUSSION

In general, to optimize adherence and treatment success, motivated and interested children and informed parents are key factors in nocturnal enuresis [1]. It is reported that the rate of spontaneous resolution is approximately 15% per year in nocturnal enuresis [5]. In the treatment of nocturnal enuresis, motivational and alarm therapies have a better outcome than drug therapy alone. Desmopressin is commonly used as a first-line drug. In resistant cases, other drugs such as anticholinergics, imipramine, and sertraline are used [1,3]. In a total of 1,780 out of 2,440 children who were enrolled receiving an active drug other than desmopressin or a tricyclic, 31 different drugs or classes of drugs such as indomethacin, diazepam, mestorelone, atomoxetine, diclofenac, amphetamine, oxybutynin, etc., were tested. Based on the findings, it was noted that there was not enough evidence to judge if the included drugs cured bedwetting when used alone [6]. In accordance with the literature, in our study, 53.8% and 92.3% of patients improved by motivational therapy and oxybutynin, respectively.

Lake [7] reported that enuresis improved in a patient with thyrotoxicosis after alprenolol, a non-selective beta blocker, as well as a serotonin 1A and serotonin 1B receptor antagonist. Enuresis relapsed after discontinuation of alprenolol [7]. Enuresis ceased in a 17-year-old girl with hyperthyroidism after propylthiouracil and propranolol therapy [8]. Meir et al. [9] reported a 9-year-old boy who suffered from hyperthyroidism and a new appearance of enuresis. Eight weeks after initiation of thiamazol and propranolol, the patient had normal hormone levels and no bedwetting. Prepulse inhibition—measured as a parameter of central control—increased during the course of therapy. They noted that the increase in prepulse inhibition is an indication that enuresis in hyperthyroidism could be as a result of a temporary loss of central control on brainstem reflexes [9]. In a series of 13 children with spinal lesions, a double-blind, cross-over study of alprenolol versus placebo was performed during conventional continence training. The number of "dry periods"; however, did not differ during the alprenolol and placebo periods [10]. The authors noted that one reason for the lack of clinical effect may be that the drug simultaneously blocked the beta receptors in the corpus-fundus of the bladder, thereby decreasing the volume capacity [10]. Walter et al. [11] reported that two female patients with adult enuresis and enuretic syndrome were cured of their voiding disorders after treatment with carbimazole and propylthiouracil for hyperthyroidism. They were without symptoms at follow-up of 5.5 years and 1.5 years later. In the latter study, a relation between thyroid and bladder function is suggested, which calls for further investigation in a controlled study [11]. Based on the above literature data, we think that there is a close relationship between enuresis and hyperthyroidism, and the same pathogenesis is responsible for both conditions because both diseases were noted in the same patients and responded well to beta-blocker therapy. However, 90% of our patients did not improve with propranolol therapy. On the other hand, we believe that primary nocturnal enuresis was due to delayed maturation of brainstem reflexes.

Migraine and nocturnal enuresis have striking similarities. Both have unknown pathophysiology and are considered multifactorial, with neurobiological, genetic, and behavioral aspects involved. The same neurological structures thought to be involved in the pathogenesis of a migraine are also thought to be involved in nocturnal enuresis [12]. Lin et al. [12] showed that nocturnal enuresis is a precursor of migraine and a migraine comorbid condition, which supports a pathophysiological linkage between the two conditions. Carotenuto et al. [13]

suggested that primary nocturnal enuresis could be considered as migraine equivalent, such as a "periodic syndrome," and the treatment and care of migraine should not exclude the causal role of sleep disorders, because nocturnal enuresis and migraine could be linked by cortical system arousal dysfunction, even if more reports are necessary. In our study, we did not investigate if our patients had a migraine or a headache. However, previously, we diagnosed a child with a migraine and primary nocturnal enuresis, whose both migraine attacks and enuresis improved after propranolol therapy. Therefore, we think that the pathophysiology and/or pathogenesis of a migraine and nocturnal enuresis are the same in some patients.

CONCLUSION

Based on our findings, we would like to emphasize that motivational therapy is the first line treatment in primary nocturnal enuresis; and oxybutynin but not propranolol is effective in patients with primary nocturnal enuresis who failed with motivational therapy.

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