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Adverse Effects of Pharmacotherapy in Children with Enuresis: A Single Centre Experience

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To assess side effects of MELT monotherapy and MELT in association with oxybutynin in children suffering from nocturnal enuresis (NE). We enrolled 340 enuretic children admitted to our Pediatric Service, Campus Bio-Medico University of Rome, from April 2014 to April 2018; 23 children were excluded. The research was structured in 2 steps. During step 1, a patient's medical history was carefully collected and physical assessment was performed. During step 2, after 3-month treatment period with MELT (Minirin/dDAVP®) at the dose of 120 mcg a day or MELT plus oxybutynin (Ditropan®), voiding calendar, adherence to treatment and any side effects were examined. The study was conducted in accordance with the Helsinki Declaration. Among 317 patients enrolled in the study, 18 male and 8 female (n=26; 26/317: 8.2%) children, with a mean age 10.86 ± 2.42 years, referred side effects: 13 cases (n=13, 13/26: 50%) treated with MELT monotherapy, 11 cases (n=11, 11/26: 42.3%) treated with MELT plus oxybutynin, 2 cases (n=2, 2/26: 7.7%) who received only oxybutynin. In our research, higher bioavailability of MELT guaranteed lower frequency of adverse effects with a spontaneous and rapid resolution. Several studies demonstrate that dDAVP is an effective and safe drug for NE and MELT formulation is actually considered for first-line therapy of NE, although further research is needed to endorse the observations of the authors.

Keywords: adverse effects, desmopressin, enuresis.

In accord with International Children's Continence Society (ICCS), nocturnal enuresis (NE) is a prevalent childhood condition that can persist into adulthood, with a profound impact on everyday life[1]. NE is an intermittent bedwetting during sleep with any frequency in children five years of age or older, without history of lower urinary tract symptoms and/or bladder dysfunction[2]. In children with daytime incontinence the broad term non-monosymptomatic nocturnal enuresis (n-MNE) is used. NE is a multifactorial disorder, with three main pathophysiological determinants that are nocturnal polyuria, detrusor overactivity and failure to awaken in response to bladder sensations[3]. NE treatment is chosen based on frequency and intensity of symptoms and the child's age and motivation. The first-line drug therapy for children with NE associated with nocturnal polyuria and normal bladder function is desmopressin (dDAVP) for a period of 3 months following by withdrawal. The response rate of dDAVP therapy is about 40-60%, however its effect may not be maintained on discontinuing treatment and symptoms have been found to recur in about

50-80% after stopping treatment[4]. Antidiuretic activity is the main therapeutic effect of dDAVP: it quickly determines a significant decrease in the number of wet nights per week compared with placebo and with homotoxicological medications[5]. The recent oral sublingual lyophilisate (MELT) represents a safe first-line drug for the NE, because its higher bioavailability ensures the same therapeutic effects of other formulations with lower doses[6,7]. In children with n-MNE, anticholinergic agents may be useful and may be prescribed in combination with dDAVP to improve bladder capacity during sleep[8].

The purpose of this research was to assess side effects of MELT monotherapy and of MELT in association with oxybutynin in children suffering from NE.

METHODS

We recruited in the study 340 children aged more than five years with a diagnosis of primary NE who did not receive NE treatment during the previous 3 months admitted to our Pediatric Service, Campus Bio-Medico University of Rome, from April 2014 to April 2018. We excluded children with secondary NE, history of urinary tract infection, nephrogenic diabetes insipidus or congenital anomalies of the genitourinary system. We asked patients and their families to take part in our research study at the end of the clinical examination and after 3 months of observation period. This study was conducted in accordance with the Helsinki Declaration. Our study was composed of 2 steps. Step 1 consisted of collecting accurate medical history of patients and performing physical assessment (especially urogenital system) including blood pressure measurement, skin markers of closed spinal dysraphism (hyperpigmented lesions, subcutaneous lipoma, dermal sinus, tails, localized hypertrichosis, aplasia cutis), presence of fecal impaction, state of bladder fullness, muscle strength or sensation differences between the lower extremities and deep tendon reflexes[9,10]. During the whole treatment period, families kept track of wet and dry nights on a calendar, and afterwards, during the follow-up period, we contacted all patients and their parents to assess adherence and response to treatment. Children with monosymptomatic NE received MELT (Minirin/dDAVP®) at a dose of 120 mcg a day for 3 months in association with dietary recommendations[11]. If medical history underlined n-MNE, oxybutynin (Ditropan®) was prescribed in combination or as monotherapy. After 3 months, voiding calendar, adherence to treatment and any side effects were examined. In our analysis we use odds ratio to determine the association between the dependent (side effects) and independent variables (gender, desmopressin in combination with oxybutynin). Results were expressed as mean ± standard deviation and percentage. For continuous variables, we used a paired-samples t-test and an independent-samples t-test, whereas for categorical variables the chi-square test. The level of significance was fixed at $P < 0.05$. Statistical analysis was performed using the Stata Statistical Software program, Release 13 (StataCorp. 2013, College Station, TX, USA).

RESULTS

We initially enrolled 340 patients; of these, 23 (6.8%) were excluded for these reasons: dDAVP treatment in the previous 3 months (15 children), lost to follow-up (5 children) and need for further period of observation (3 cases). Therefore, 317 patients were recruited in our study: 215 (67.8%) were male and 102 (32.2%) were female, between the age of 5 and 18 years (mean age 10.86 ± 2.42 years). Among 317 children enrolled in the study, 18 male and 8 female patients (n=26; 26/317: 8.2%) with a mean age 10.39 ± 2.97 years, referred side effects related to three different group of treatment. In particular:

• 13 cases (n=13/317: 4.1%, 13/26: 50%) treated with MELT monotherapy reported neurological symptoms (headache and migraine) (n=4, 4/26: 15.4%), gastrointestinal adverse effects (nausea, abdominal pain, vomiting) (n=4, 4/26: 15.4%), sleep disorders (trouble falling asleep, frequent wake-ups during the night) (n=4, 4/26: 15.4%), psychological and behavioral problems (irritability, trouble paying attention, aggression) (n=7, 7/26: 26.9%), anxiety (n=1, 1/26: 3.8%);

• 11 cases (n=11/317: 3.8%; 11/26: 42.3%) treated with MELT in association with oxybutynin reported neurological symptoms (headache and migraine) (n=3, 3/26: 11.5%), gastrointestinal adverse effects (nausea, abdominal pain, vomiting)

(n=2, 2/26: 7.7%), sleep disorders (trouble falling asleep, frequent wake-ups during the night) (n=4, 4/26: 15.4%), psychological and behavioral problems (irritability, trouble paying attention, aggression) (n=9, 9/26: 34.6%), anxiety (n=2, 2/26: 7.7%);

• 2 cases (n=2/317: 0.6%; 2/26: 7.7%) received oxybutynin and reported neurological symptoms (headache and migraine) (n=0), gastrointestinal adverse effects (nausea, abdominal pain, vomiting) (n=1, 1/26: 3.8%), sleep disorders (trouble falling asleep, frequent wake-ups during the night) (n=1, 1/26: 3.8%), psychological and behavioral problems (irritability, trouble paying attention, aggression) (n=1, 1/26: 3.8%), anxiety (n=0).

The relationship between adverse effects and age was estimated with Student t-test. The mean difference between mean age of the patients with and without adverse effects was calculated at a significance level $P > 0.05$. When side effects occurred, the patients interrupted the treatment with the complete resolution of the symptoms within 48 hours.

The relationship between the side effects and treatment with MELT was definited by the odds ratio of 0.47 with a significance level of $P = 0.2$. The relationship between the adverse effects and the combined therapy (MELT plus oxybutynin) was correlated by the odds ratio of 4.61 (IC 1.62-13) with a significance level of $P < 0.05$. The relationship between adverse effects and sex was quantified by the odds ratio of 1.30 with a significance level of $P < 0.05$.

DISCUSSION

NE is a multifactorial disorder with a genetic susceptibility. Risk factors, that can worsen NE, include family history, male gender, low socio-economic status and social disadvantage, poor school performance, sleep disturbance, overactive bladder, attention deficit/hyperactivity disorder (ADHD), costiveness[12,13]. Primary NE resolves spontaneously in high percentage and it has decreasing prevalence from childhood through adolescence (16% at age 5 years, 5% at age 10 years, 1-2% at age e”15 years). Current therapies for NE include behavioural techniques, use of alarm device, desamino-D-arginine vasopressin (dDAVP, desmopressin) treatment, anticholinergic such as oxybutynin, tricyclic antidepressants such as imipramine or an association of therapy. In our research, we analysed the side effects of pharmacological treatment in children with NE. Our data shows an absolute risk of 7.6% for the occurrence of adverse effects with dDAVP treatment in monotherapy or in combination with oxybutynin. According to a recent review, the overall incidence of adverse effects among 1083 children who received dDAVP for NE was 5%[14]. Several factors can explain the gap between the incidence rates of our sample and this reference study, first of all the difference between number and age of patients enrolled (1083 children and adults in the review vs 317 children in our study). Furthermore, the incidence data of our research refer to MELT monotherapy or in combination with oxybutynin, whereas Van Kerrebroeck utilized dDAVP monotherapy in tablet or nasal spray formulation in patients suffering from monosymptomatic NE[14]. Any statistically significant relationship between dDAVP therapy and other variables such as sex ($P = 0.61$) and age of patients ($P = 0.32$) was not detected in our study. dDAVP is an alternative to NE bed alarms for children and their families and it is a first-line treatment for NE in children whose bed-wetting has not resolved with behavioural techniques (advice about fluid intake, toileting, appropriate reward system). The starting dose of MELT is 120 mcg; if necessary, after 10 to 14 days, the dose might be increased to a maximum dose of 240 mcg. dDAVP acts on V2 receptors expressed in the renal collecting duct, promoting water reabsorption and leading to decrease urine output. Dilutional hyponatremia is the most serious adverse effect: it can occur when excess fluids are taken in the evening hours. Physicians should warn families and patients about the risk. Guidelines recommend limiting ûuid consumption starting 1 hour before taking the drug and until the child wakes the next morning. The ICCS guidelines recommend limiting a child’s evening intake to 200mL. Treatment with dDAVP should be interrupted during episodes of fluid and electrolyte disorders (e.g. fever, recurrent vomiting or diarrhea, vigorous physical activity or conditions associated with increased water consumption). The most common side reactions encountered in our research were psychological and

behavioral problems, gastrointestinal disorders, headache and sleep disorders. These reactions are more numerous and debilitating than those mild side effects frequently reported in the literature[14]. They are probably correlated with excessive fluid intake or an inappropriately high dose of drug, even though there is no experimental evidence for this hypothesis. Currently, dDAVP is available in various formulations. Research in the literature and post-marketing surveillance about the safety profile of the oral and MELT formulations underline a lower incidence of adverse effects (expecially hyponatremia) of these two formulations compared to nasal spray. The longer duration of action (up to 24 hours) and/or interindividual pharmacokinetic differences between different formulations can probably explain this finding. Finally, an important statistical issue to consider is the association between side effects and combination therapy with dDAVP plus oxybutynin ($P < 0.001$), because the latter is a possible causal factor (OR = 4.61). Oxybutynin is an anticholinergic drug that acts on M1, M2 and M3 receptors expressed in bladder smooth muscle; it may be liable for adverse effects including xerostomia, nausea, vomiting, costiveness, headache and insomnia. Moreover, oxybutynin, perhaps causing xerostomia, stimulates increased absorption of fluids, which is one of the major underlying mechanisms liable for the occurrence of desmopressin negative effects. The incidence rate of adverse effects of different formulations of dDAVP is not simple to assess and it is often confused because dDAVP is sometimes used concomitantly with other treatments. Our results hypothesize a low incidence of adverse effects related to MELT compared to an oral administration. Moreover, the incidence of these effects increases if MELT treatment is combined to oxybutynin.

CONCLUSION

In our study, we report that MELT formulation, thanks to its higher bioavailability, ensures lower frequency of adverse effects which resolved spontaneously and rapidly. Several studies demonstrated that dDAVP is an effective and safe medication and MELT formulation is actually considered for first-line therapy of NE. Further research on large scale is needed to confirm the authors' observation.

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