EFFECTIVENESS OF DESMOPRESSIN AND OXYBUTYNIN HCL IN THE TREATMENT OF NOCTURNAL ENURESIS

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Abstract

Background: Nocturnal enuresis is an innocent but distressing disorder occurring in many children which may lead to poor self-esteem.

Objectives: To evaluate the response of a group of children with nocturnal enuresis to intranasal Desmopressin or oral Oxybutynin HCl, and compare the response to both drugs.

Subjects & Methods: This prospective study was done over 4 weeks period. Patients were 25 children aged 6-13 years with severe nocturnal enuresis; they were divided into two groups. First group = 17 children received intranasal Desmopressin 20 µg; if no response, increased to 40 µg. Second group = 8 children received Oxybutynin HCl orally one tablet (5 mg), if no response; increased to 2 tablets. Response was regarded as a decrease in number of wet nights per week, and divided into 3 categories: full responders with 0-1 wet night /week, intermediate with 2-3 wet nights/ week and non-responders with > 3 wet nights / week.

Results: The response rate to Desmopressin was 82.4%; 53% of them were full responders, while the response rate to Oxybutynin HCl was 50%; 25% of them were full responders. The mean number of wet nights/week for the total 4 weeks therapy for the Desmopressin group was (2.1±1.9) and for the Oxybutynin HCl group was (3.8±2.8). There was a highly significant difference before and after therapy in the Desmopressin group ($P<0.001$). None of the children developed side effect to Desmopressin, one child had side effect to Oxybutynin HCl.

Conclusion: For short-term therapy over 4 weeks, Desmopressin was safe and highly effective in the treatment of nocturnal enuresis. Oxybutynin HCl was less effective with some side effect. Further studies for longer periods are needed.

Key words: Nocturnal enuresis, Desmopressin, Oxybutynin HCl

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[1]Introduction

Nocturnal enuresis (NE) is an innocent but distressing disorder occurring in many children. It can negatively affect early childhood and can last until adulthood, this may result in emotional stress, behavioral problems and poor self-esteem[1,2]. Nocturnal enuresis arises through the ill-functioning of one or more of the following three mechanisms: a lack of Vassopressin release during sleep, bladder instability, and/or an inability to arouse from sleep to bladder sensations[2-5]. Genetic factors are the most important in the etiology of NE, but somatic and psychological environmental factors have a major modulatory effect[6]. The treatment approach for NE is controversial due to lack of consensus to the exact causes of NE, despite various treatment modalities; pharmacotherapy still appears to be the common choice[7]. The drugs used for the treatment of NE are mainly Tricyclic antidepressants, Anticholenergics and synthetic Vassopreessin (Desmopressin)[8].

Aims of the Study: On a short-term period of 4 weeks therapy:

1. Evaluate the response of a group of children with NE during administration of intranasal Desmopressin or oral Oxybutynin HCl.
2. Compare the response to the two mentioned drugs.

Patients & Methods

Twenty five children with primary NE (PNE) formed the bases of this prospective study for the period between October 2001 to July 2002, they all attended the pediatric nephrology clinic in Al-Kadhimiya Teaching Hospital, their age ranged from 7 years to 13 years, all suffered from sever PNE, defined as minimum of 3 wet nights per week[9], all of our patients had daily bed wetting; so the mean number of wet nights per week = 7.0±00, and they were enuretic since birth so regarded as primary type of enuresis[8,10].

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A complete case history was taken, physical examination, urinalysis, specific gravity and urine culture were performed to all patients, and telephone number (if present) was taken. Patients were excluded who had daytime incontinence, urinary tract infection or urinary tract abnormalities. The patients had not been taken any medications two weeks before entry to the study. The patients were studied during a period of 4 weeks; they were randomly divided into 2 groups:

First group: consisted of 17 children who received intranasal Minirin (which contains Desmopressin, a structural analogue of the natural hormone Arginine Vassopressin, Ferring AB, Sweeden). Initial dose was 20 μg, increased when no response to the maximum of 40 μg, as a recommended effective dose[11].

Second group: consisted of 8 children who received anticholenergic oral tablets (Oxybutynin HCl), initial dose one tablet of 5 mg, increased when no response to a maximum of two tablets (10 mg)[12].

All patients were assigned diary cards, and recording dry and wet nights was done by the parents. For both groups, each patient was given the lowest dosage of the drug that reduced the number of wet nights by 50% or more, if this aim was not achieved, the dose of either drug was increased to the maximum recommended effective dose of that drug.

Throughout the whole study, the response to both drugs was registered as the decease in the number of wet nights per week. According to their response, the patients in both groups were divided into three categories:

Full responders: with one or none wet nights per week.

Intermediate responders: with 2- 3 wet nights per week.

None responders: with more than 3 wet nights per week.

Patients were followed during the study and watched clinically for adverse effects of the drugs. Final results were returned by either parents of the patients, and some results were obtained by phone calls.

Paired t test was used to compare between the number of wet nights per week before and after therapy for both groups, P value was considered significant if (<0.05).

Results

Patients were 25 children, males were 14 and females were 11. Male to female ratio was (1:0.78). Age range of the study group was 6-13 years. Family history of enuresis was recorded in 20 children (80%), and was negative in 20%.

Results of the first group: All the 17 children were started with 20 μg intranasal Desmopressin at bed time, at the end of 1st week, 4 of them had no response, so increase the dose for them to 30 μg. At the end of 2nd week of therapy, 2 of those 4 children still had no response so increase the dose further to maximum of 40 μg, but by the end of 4th week of therapy, those 2 children still had no response. We had one patient who was intermediate responder at the start of therapy so no further increase in the dose was given to her, but she turned to be non- responder at the 4th week of therapy.

So in total at the end of 4 weeks therapy, 3 children (17.6%) were non responders, the rest of 14 children were responders (82.4%), 9 of them (53%) were full responders and the other 5 (29.4%) were intermediate responders (Table 1).

Table 1: Response rate to intranasal Desmopressin of 17 children in the first group

Response	Number	%
Full responders	9	53
Intermediate responders	5	29.4
Non responders	3	17.6
Total	17	100

Results of the second group: All 8 patients were given Oxybutynin HCl 1 tablet (5 mg) orally at bed time, by end of 1st week of therapy, 5 of them were non – responders, so increase the dose for them to maximum of 2 tablets (10 mg), at end of 2nd week of therapy, one of those 5 children became full responder while the other 4 children still were non – responders and continue so to the end of 4th week of therapy.

So in total at the end of 4 weeks therapy, 4 children were responders (50%), 2 of them were full responders (25%) and the other 2 were intermediate responders (25%) while the rest of 4 children (50%) were non responders (Table 2).

Table 1: Response rate to oral Oxybutynin HCl of 8 children in the second group

Response	Number	%
Full responders	2	25
Intermediate responders	2	25
Non responders	4	50
Total	8	100

In the 1st group on Desmopressin, the mean number of wet nights /week decreased significantly in the 1st week of therapy from 7±00 before therapy to 2.6±2.2 (P<0.05). Further results showed that the mean number of wet nights/week for the 2nd, 3rd and 4th weeks of therapy decreased significantly to 1.8±1.9, 1.8±1.8 and 2.2±2.3 respectively (P<0.05 for all).

Results of the 2nd group on Oxybutynin HCl showed a decrease in the mean number of wet nights/week from 7±00 before therapy to 4.2±2.4, 3.9±2.9 and 3.9±2.9 in the 1st, 2nd and 3rd weeks respectively, however statistically were non-significant (P>0.05), but there was a significant decrease in the number of wet nights on the 4th week to 3.6±2.7 (P<0.05), (Figure 1).

The mean number of wet nights/week for the total 4 weeks therapy for the 1st group was 2.1±1.9, which was highly significantly different from the mean observed before Desmopressin therapy (P<0.001), (Figure 2).

On the other hand, the mean number of wet nights/week for the total 4 weeks therapy for the 2nd group was 3.8±2.8 which gave a significant difference from the mean before oxybutynin therapy (p<0.05), (Figure 2).

None of the children treated with Desmopressin had any side effect, only one girl 6 years old treated with oxybutynin HCl developed tachycardia and flushing when received 2 tablets and she was non responder so the drug was stopped.

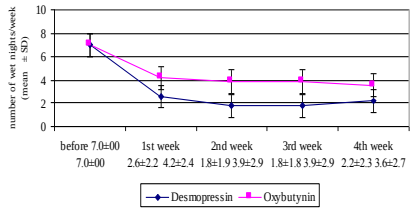

Figure 1: Mean No. of wet nights per week before and during first, second, third, and fourth weeks of therapy for both Desmopressin and Oxybutynin HCl groups

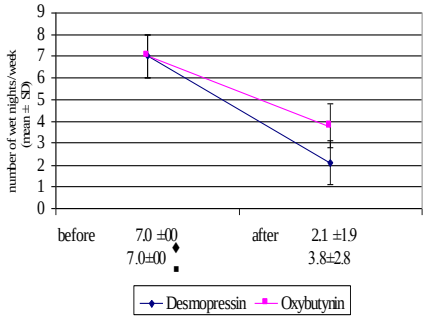

Figure 2: Mean No. of wet nights per week before and total 4 weeks therapy for both Desmopressin and Oxybutynin HCl

Discussion

Similarly to most studies, we had male predominance over females[8,10,12,13]. Compared to our results, lower percentages of family history of enuresis was recorded by other reports[9,10,14]. The high percentage of family history of enuresis among our cases might be explained by high incidence of marriages between relatives in our society, it was estimated that as the closeness of the genetic relationship decrease, the incidence of enuresis diminishes[12].

In our study, the response rate to intranasal Desmopressin was (82.4%), this high response rate was agreed upon by many other studies from different regions in the world with percentages ranging between (70%-85%)[15-21]. The effect of Desmopressin on NE is due to it's antidiuretic properties and reduction of nocturnal urine output[22].

More than half of the patients in the 1st group were full responders to Desmopressin (53%), 2 other studies reported nearly similar figures[9,23]. In the 1st group, a highly significant difference in the mean number of wet nights per week before and after Desmopressin therapy was detected. In a literature search which was performed for the period Jan. 1966 to August 1992 including 14 studies; 11 of them showed a significant decrease in the mean wet nights per week on Desmopressin therapy[13], also it was reported in a recent large search on 21 randomized trials involving 948 children from 1985-1996 treated with Desmopressin, that it was effective in reducing bedwetting in a variety of doses and forms[24].

Among the 2nd group, the response rate to Oxybutynin HCl was obtained in only half of the patients, a response rate to Oxybutynin HCl of 54% was recorded in a study from Italy[21], and a response rate of 10%-50% was reported by a recent study from Tokyo[25].

Oxybutynin HCl effect in NE is due to it's anticholinergic activity and some direct muscle relaxant properties and inhibits the muscarinic action of acetylcholine on smooth muscles and increased bladder retention[8,12,14,22]. Although the difference between mean number of wet nights per week of the total 4 weeks therapy before and after Oxybutynin HCl therapy was statistically significant, but it was not highly significant as the difference obtained in the Desmopressin group as shown in Figure 2 .

Varan *et al* reported that Oxybutynin HCl did not cause a significant difference in the number of dry nights among his study group[26].

Kosar *et al* in their study found that the majority of patients (88.3%) responding to Oxybutynin HCl; were those with inadequate bladder storage function (IBSF), while the treatment in patients with normal bladder function was generally unsuccessful, also he found a significant decrease in mean number of wet nights per week of the two groups after Oxybutynin HCl therapy compared to the pretreatment value, but the difference was highly significant in the group with IBSF[14].

Similarly in a wide study from Sweden, they found that children responding to Oxybutynin HCl have small bladders and probably hyperactive detrusor muscles[27].

Most studies from different regions reported no adverse effect to Desmopressin intranasal therapy[13,15,16]. Side effects to Oxybutynin HCl therapy was recorded in 5 of 9 patients in Varan *et al* study[27].

Kosar *et al* in their study reported dryness of the mouth in 50%, constipation in 11.8% and flushing in 5.9% of treated patients with Oxybutynin[14].

Neveus *et al* in their study reported that two main types of NE can be discerned: (1) Diuresis dependant enuresis in which children void because of excessive nocturnal urine production and impaired arousal mechanism, (2) Detrusor dependant enuresis, those children void because of detrusor hyperactivity and impaired arousal mechanism. The main clinical difference between the two groups is that Desmopressin usually effective in the former but not in the later type, accordingly Desmopressin was applied as first line therapy, anticholinergic drugs as the second line treatment[5].

Conclusion: Intranasal Desmopressin; when used daily for a period of 4 weeks in the treatment of nocturnal enuresis was safe, useful and highly effective in reducing the number of wet nights of enuretic children. Oxybutynin HCl was less effective in the treatment of NE with less significant decrease in wet nights than Desmopressin with few side effects.

Recommendations: Further studies for longer periods of treatment are needed in order to assess the long term efficacy of both drugs.

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