The Role of Addition of Diclofenac Sodium to Imipramine in Treating Children with Nocturnal Enuresis

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ABSTRACT:

BACKGROUND:

Nocturnal enuresis presents a common medical problem all over the world, over many years various therapeutic options have been tried; none was proved to be superior, because the defect occurs at many levels in the urinary tract and its neuronal control. Nowadays prostaglandins have been proved to play a role at renal, bladder, urethral and sympathetic control of urinary system.

OBJECTIVE:

We evaluated the role of diclofenac sodium when added to the conventional imipramine therapy in treating patients with primary nocturnal enuresis.

PATIENTS AND METHOD:

70 children complaining of nocturnal enuresis were enrolled in this study, half of them were given imipramine alone and the other half were given a combination of imipramine and diclofenac sodium at night before retiring to bed, and the number of wet nights per week was recorded on a calendar sheet by the parents over 4 weeks, those who showed more than 50% reduction in the number of wet nights a week were regarded as responders, who were followed after cessation of treatment over another 6 weeks to look for relapse.

RESULTS:

Of the patients treated with imipramine alone 57.14% (20/35) showed more than 50% decrease in the number of wet nights weekly compared to those treated by imipramine and diclofenac sodium who showed 84.84% (28/33) response rate (> 2.5 SE of difference between responding proportions). The relapse rate after stopping treatment was 60% (12/20) in the first group compared to 32.1% (9/28) which exactly two times the SE of difference between relapsing proportions.

CONCLUSION:

The addition of diclofenac sodium to imipramine in treating patients with primary nocturnal enuresis might have caused a highly significant higher response rate and a fairly significant lower relapse rate after cessation of treatment.

KEY WORDS: imipramine, diclofenac sodium, nocturnal enuresis.

INTRODUCTION:

According to the international children's continence society (ICCS), nocturnal enuresis (NE) means simply bedwetting only, day and night wetting or isolated day wetting is called incontinence. NE is considered primary if the child had never experienced a period of dryness of 6 months or more, and secondary if such a dry spell is experienced by the child any time before[1,2]. NE affects 6-10% of children at the age of 7 years, 15% of whom remit every year. According to these figures, the risk of an enuretic child to continue to have the disease into adulthood is about 3% if was not treated, a prevalence similar to what was reported by Forsythe and Redmond (1974)[2].

Pathophysiology:

NE is a heterogeneous disorder that can be caused by any one or combination of several pathophysiological mechanisms that result in either increased nocturnal urine production or a small functional bladder capacity or both [4].

Nocturnal polyurea:

A marked circadian rhythm of urine production is developed early in life with a remarkable reduction in diuresis at night up to 50% of day time levels [5,6]. This rhythm is controlled by elevated nocturnal levels of hormones that regulate free water excretion (arginine-vasopressin) or solute excretion (angiotensin II, aldosterone)[7].

As early as the 1950's, it was observed that enuretic children had a significantly larger nocturnal urine production than non-enuretics, this nocturnal urine production varies from night to night[8], and significantly larger on wet nights[2], this is supposed to be due to lack of normal nocturnal rise of arginine-vasopressin[9]. The mechanism of increased solute excretion at night is

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some patients is unclear, and the roles of angiotensin II, aldosterone, and various prostaglandins are still under investigations[2], however, it is stated that in adolescence the reduction of nocturnal urine production occurs mainly due to a decrease in urine sodium excretion rather than a rise in antidiuretic hormone secretion[5,7,10]. Presently, there is a consensus that relative nocturnal polyuria plays an important role in the pathogenesis of NE in two thirds of enuretic patients regardless of age[11]. There are various lines of evidence supporting the role of prostaglandins in renal vasodilation and increased renal blood flow and urine production. Frøkiær and Sørensen (1995) demonstrated an increase in PGE_2 excretion in the urine from the contralateral kidney after unilateral ureteric obstruction[27,22]. In addition, studies have shown that the increase in PGE_2 and the vasodilation of the obstructed kidney could be blocked by indomethacin, a prostaglandin synthesis inhibitor [28,22].

Bladder function: since many years, the urinary bladder capacity and function had been in focus regarding their possible role in NE. A practical evaluation is what's called functional bladder capacity (FBC), which is the largest daytime void on a frequency-volume chart excluding the first morning void[2]. When the FBC is below 70% of the predicted capacity for age, it suggest a little role of nocturnal polyuria in the pathogenesis of NE[12], however nighttime and daytime FBC are not equall, nighttime FBC in non-enuretic children is 1.6-2.1 times larger than daytime FBC [13], but this is not the situation in enuretic children. As many as one third of all enuretic children have a nocturnal detrusor over activity that necessitates a specific therapy in order for enuresis to resolve[11,16].

Prostaglandins(PG) may have a function in maintaining vesical tone, PG of both F and E series cause bladder muscle to contract, PGF2α being the most potent of all[17].

PATIENTS AND METHOD:

During the period from Dec. 2008 until April 2009, a total of 70 patients were included in this study, inclusion criteria were primary MNE with at least 5 wet nights a week, age between 8-16 years, with no history of urological abnormalities or chronic constipation. All patients were assessed by full history and physical examination, blood glucose level, renal function tests, and abdominal ultrasonic examination. Patients with history of asthma, renal, cardiac and gastrointestinal disorders, and drug allergy were excluded from the study.

An informed consent was obtained from the parents who were then instructed to record wet and dry nights in a calendar sheet over the study period, then patients were followed up on weekly basis.

Patients were randomized in to 2 groups of 35 patients each, first group patients were given a tablet of 25 mg imipramine (tofranil) each night before retiring to bed; the (imipramin group).The second group patients received a combination of imipramin 25 mg tablet and diclofenac sodium (voltaren) 25 mg tablet in the same manner; the (combination therapy group). All patients were kept on treatment continuously over the next 4 weeks, and their wet and dry nights were recorded on the calendar sheet by the parents and followed up by doctors on weekly basis.

Patients who started to have two wet nights weekly or less are regarded as responders, while those who still wet their beds three times weekly or more are considered non-responders, according to the definition of response by the ICCS.

The responders in both treatment groups were followed after cessation of treatment for another 6 weeks to observe for relapse.

Data then collected and statistically analyzed using the standard error of difference between proportions as a level of significance.

RESULTS:

Results of data analysis are summarized in table (1), two patients of the groups treated by imipramine and diclofenac sodium were lost during follow up and were omitted.

Table (1) clearly demonstrates a comparable age and sex distribution within both groups (10.7 vs. 11.4 years).

Of the 35 patients treated by imipramine alone 20 cases (57.14%) responded by a reduction of wet nights to less than half of the pretreatment number, 12 (60%) of whom relapsed after 6 weeks of cessation of treatment.

For the 33 patients treated by imipramine and diclofenac sodium, 28(84.84%) responded to treatment, and 9 (32.14%) relapsed following cessation of treatment.

The standard error of difference between proportions of response in both groups was calculated and found to equal 1.45, so the difference in response rate between the two groups is more than 2.5 times this standard error, which signifies a highly significant higher response rate in the group treated by both imipramine and diclofenac sodium compared to that treated by imipramine alone.

On the other hand the standard error of difference between proportions of relapse in both groups also was calculated and found to equal 14.0, according

to this result, the difference in relapse rate between the two groups is twice the standard error, which indicates a fairly significant lower relapse rate in the group treated by imipramine and diclofenac sodium than that treated by imipramine alone.

Table 1: Age and sex distribution, response and relapse rates in both groups

group	No. of patients	Average age	sex		Response			Relapse		
			male	female	no	%	SE	no	%	SE
imipramine	35	10.7	19	16	20	57.14	8.36	12	60	10.95
Imipramine+ diclofenac	33	11.4	19	14	28	84.84	6.24	9	32.1	8.82

The standard error of proportion of response between the two groups equals 1.45
The standard error of proportion of relapse between the two groups equals 14.00

DISCUSSION:

Enuresis presents a challenging problem to the practicing physician and a source of tension and stress for the patients and their parents; it is encountered in all societies and causes much dissatisfaction between the treating doctor and the parents.

Imipramine, an antidepressant, is commonly used for the management of enuresis by urologists, pediatricians, and general practitioners in Iraq, it is already stated that only about 50% of patients respond to it [19,20] and the reported lasting cure rate is only around 17% [21].

In this study we tried to explore the role of adding diclofenac sodium to imipramine in treating enuretic patients making use of new studies that analyzed the role of prostaglandins on the renal system.

The central conclusion that can be drawn from the statistical analysis of the data collected is that the addition of diclofenac sodium to imipramine therapy for enuretic children has significantly raised the response rate to treatment demonstrated by more than 2.5 times the standard error elevation in the response rate of patients treated by a combination of imipramine and diclofenac sodium compared to those treated by imipramine alone, and a fairly significant drop in relapse rate after cessation of therapy, shown by the 2 times standard error reduction in relapse rate between the two groups.

Diclofenac sodium, being a NSAID acts through the inhibition of synthesis and release of prostaglandins; this may produce the anti-enuretic effect at different levels:

1. At the renal level, through decreasing the nocturnal glomerular filtration rate, and urine output [23].
2. At the bladder level, by reducing the intravesical pressure and increasing the threshold volume of micturition [24].
3. At the urethral level: elevating the urethral pressure and resistance[25].
4. At the sympathetic nervous system level: prostaglandins are known to be potent inhibitors of noradrenaline release and subsequent response[26].

Metin and Aykol (1992) compared the use of diclofenac sodium suppositories with placebo in treating children with NE and found a significant response rate in those treated with diclofenac sodium compared to placebo [3], on the other hand, Natochin and Kuznestova reported a response rate to diclofenac sodium treatment in enuretic children of only 33%[14]. Hosseini and coworkers used a combination of diclofenac sodium and imipramine and compared it to imipramine alone therapy, they found a significant improvement in the response rate in the combination therapy group, as well as a lower relapse rate after cessation of therapy [15].

A major limitation in our work was the number of cases included and studied, studying such a common medical problem in the community requires a larger number of cases and a good commitment of parents to record the wet and dry nights on the calendar sheet and present them to the doctors weekly for follow up.

The impact of other factors affecting the response rate tried to be minimized; of these is the drinking of water and other beverages at night, we advised the parents not to change the usual child's habit of drinking, and not to change the child's habit of sleep by avoiding alarm systems through out the study time.

Although the improved response rate to a combination of imipramine and diclofenac sodium compared to imipramine alone is obvious, the lower relapse rate after treatment cessation needs to be further evaluated because we did our monitoring for such an event over a relatively short period (6 weeks) due to loss of contact with the patients after

this period since most parents stop seeking medical help once their children stop wetting their beds, for this we advice more prolonged studies on this issue.

CONCLUSION:

The oral form of diclofenac sodium is effective and should be kept in mind as a good alternative or supplementarydrug in the treatment of primary enuresis.

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