The Turkish Journal of Pediatrics 31:215 - 220, 1989

TREATMENT OF NOCTURNAL ENURESIS: A PLACEBO-CONTROLLED TRIAL WITH PIRACETAM, DIPHENYLHYDANTOIN AND PSYCHOTHERAPY*

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Key words: diphenylhydantoin, enuresis, piracetam, psychotherapy

Various types of medication and methods have been used in the management of nocturnal enuresis (NE), even though this condition mostly subsides spontaneously with age[1-3]. Considerable controversy has arisen regarding the therapeutic effectiveness of piracetam[4,5]. This placebo-controlled study was undertaken in a bid to settle the conflict regarding the use of piracetam in the treatment of NE.

Material and Methods

Of 730 outpatients (374 males and 356 females) aged between 6-14 years who were questioned at the Ankara S.S.K. Children's Hospital for NE, 201 children (117 males and 84 females) were found to be enuretic.

One-hundred enuretic children were randomly selected whose history, physical examination, urinalysis and urine culture were negative for diurnal enuresis, encopresis, urinary tract infection and organic defects. There were 27 patients who had been excluded from the study because they either were not cooperative or failed to come for their visits to the hospital. Electroencephalograms (EEG) of all the patients and 20 of the non-enuretic children (controls) were blindly evaluated. The intelligence quotient (IQ) of 56 enuretic and 16 non-enuretic children, who had been randomly selected were determined by using Wechsler's Intelligence Scaling Score (WISC). Also the IQs of 21 patients receiving piracetam were measured at the end of the eighth week of the study.

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The patients were randomly assigned into four of the following treatment groups: Group I consisted of 18 patients who had received piracetam (Nootropil^{R}) in a single dose of 20 mg/kg (maximum 800 mg) at bedtime. Group II consisted of 15 patients who had received play or supportive therapy[6,7] for ten weeks in weekly sessions, each session lasting for at least 40 minutes. Group III (combined treatment group) consisted of 12 patients who had received both drug and psychotherapy for eight weeks. Group IV consisted of 14 patients who had received a single dose placebo at bedtime. Group V consisted of 14 patients who had received diphenylhydantoin (Epdantoin^{R}) in a dose of 5 mg/kg/day. Although the epileptic patients were not considered to be enuretic, the EEGs of the 14 enuretic children in Group V revealed epileptic abnormalities.

All patients were seen at the end of the second, sixth and eighth weeks. Therapeutic effectiveness was graded as follows: 0-no improvement, 1-partial improvement, 2-complete cure. The classical Chi square, Fisher's exact test and variance analysis were used to evaluate the differences.

Results

Of seven hundred and thirty children aged between six and 14 years (mean: 9.2 ± 2.17) who were questioned, 201 (27.5%) children (male/female ratio: 58/42; mean age: 8.5 ± 2.3 and 8.4 ± 1.9, respectively) were found to be enuretic. Of these, 31 percent were males and 24 percent were females, and 10.1 percent were between 6-7 years of age and 3 percent were over 11 years of age.

EEG abnormalities, e.g. random spike discharges, diffuse high voltage slow waves and "build-up" phenomenon, were found more frequently in the enuretics (29% of the enuretics and none of the controls). The IQs of the enuretics were found to be significantly lower ($p < 0.05$) than those of the non-enuretics (compared with controls it was 94.68 ± 2.43 and 104.25 ± 2.83, respectively). The EEGs and IQs of all treatment groups (excluding the EEGs of Group V) showed no statistically significant ($p > 0.05$) differences. The IQs did not significantly affect the therapeutic responses ($F = 0.139$; $p > 0.05$). No significant differences in the IQs of Group I were observed after treatment.

Therapeutic response is summarized in Table I. A complete cure observed in Group III was significantly ($X^2 = 10.86087$; $p < 0.05$) higher than the other groups. If we consider partial improvement a positive response, then both psychotherapy and combined therapy (Groups II and III) can be said to have a significant effect ($X^2 = 1.376633$, $p < 0.05$). There were no significant differences between Groups I, IV and V. No side-effects were observed except for mild headache and nausea during the course of treatment with piracetam.

TABLE I: Summary of Therapeutic Responses in the Treatment of Nocturnal Enuresis

Group	Drug and Method	Response+ 0 n	0 %	1 n	1 %	2 n	2 %	Total
I	Piracetam	9	50	7	39	2	11	18
II	Psychotherapy	–	–	8	53	7	47	15
III	Combined group	–	–	4	33	8	67++	12
IV	Placebo	4	28	5	36	5	36	14
V	Diphenylhydantoin	4	28	6	44	4	28++	14

+See text, ++X^2= 10.86087, $p < 0.05$

Discussion

NE is defined as involuntary "bedwetting" if it occurs at least twice a month after an age (mostly five years) when bladder control is expected to have been attained[8]. Although there is no general agreement concerning the age at which enuresis should be considered abnormal[9], some authors propose that children should not be labelled enuretic unless wetting persists at least once a week past the age of five years in girls, and from six to ten years of age in boys[3].

It has been established that the presence of stress factors occurring during the developmental period, that is, between the ages of two to four[10], a time at which bladder control has not yet been fully acquired, may cause NE which may be improperly diagnosed as "primary" NE. Therefore, it is difficult to classify enuresis as primary or secondary simply by evaluating a period of six or twelve months of "dry nights"[3]. For this reason we did not divide our patients into groups of primary and secondary enuresis.

Jarvelin et al[11] found that the incidence of enuresis among low birth-weight children was greater than among normal birth-weight children, and that children with both diurnal and nocturnal enuresis were found to have the lowest birth-weights among enuretics. They assumed that the reason for this may be that neurological damage is most obvious in low birth-weight children. Jarvelin et al[11] referred in his study to Shaffer et al[12], who suggest that enuresis can be classified into two groups: those with and those without associated neurodevelopmental abnormality. They assumed that neurologically damaged children experience both diurnal and nocturnal wetting while children with delayed maturation experience mainly night-wetting with genetic predisposition. Inoue et al[13] reported that the rhythmic slow wave observed in nocturnal sleep encephlograms in children with

NE may also be caused by the immaturity of the sleep mechanism in enuretic children. Some authors[14,15] have suggested that epilepsy plays a role in the etiology of enuresis, while others[16,17] do not accept it as being a nocturnal manifestation of classical convulsive epilepsy. Kaada and Retvedt[18] assumed that epilepsy and primary NE may be the effect of the same higher level brain dysfunction or of cortical instability resulting from delayed maturation. Our results failed to show any beneficial therapeutic effectiveness of antiepileptic treatment with diphenylhydantion in NE after a period of 8-10 weeks.

Several drugs and methods have been suggested in the management of NE which have had varying rates of success. Chemotherapy using imipramine and desamino-D-arginine-vasopressin and "alarm and conditioning" therapy have been found to be most effective[3,4,8,19-26]. Piracetam, a nootropic agent, is claimed to improve alertness thereby speeding up mental performance, acts on the cortical control of subcortical brain structures, has a certain protective effect against the consequences of induced brain hypoxia, and has an enuretic activating effect on the cortex[5,27]. Pogady et al[5], who treated 37 children with piracetam, reported a rate of improvement of more than 50% in 81% of the patients, while Yurdakok et al[4] reported no significant therapeutic effects after six weeks treatment with piracetam.

In the present study piracetam (Nootropil^{R}) was administered to 30 patients (12 patients were given the drug in combination with psychotherapy), and we found that the therapeutic effects did not differ from those given the placebo.

In our patients a complete cure rate of 67% and a partial improvement rate of 33% were achieved with play and/or supportive therapy combined with piracetam (the same as the placebo group).

We recommend play and/or supportive therapy in association with a placebo as the first step in the management of NE which is in agreement with Novello[3] and also other researchers[28], who suggest that medication should never be prescribed in isolation in treating this condition.

Summary

The study population consisted of 100 children with nocturnal enuresis (NE) aged between six and 14 years, who had been randomly selected amongst the enuretic outpatients at the Ankara S.S.K. Children's Hospital. A placebo-controlled evaluation of piracetam, diphenylhydantoin and psychotherapy was carried out. At the end of the eighth week of the study, it was discovered that the therapeutic effects observed in the patients administered piracetam did not differ from those given the placebo. Therefore, we recommend that psychotherapy in association with a placebo be the first step in the treatment of NE children.

Acknowledgment

We wish to thank Dr. Osman Saka, Department of Biostatistics, Hacettepe University, Ankara, for his statistical evaluations and analyses.

REFERENCES

1. Bakwin H. Enuresis. *Am J Dis Child* 123:86, 1972.
2. Werry JS, Cohrssen J. Enuresis: an etiologic and therapeutic study. *J Pediatr* 67:423, 1965.
3. Novello AC, Novello JR. Enuresis. *Pediatr Clin North Am* 34:719, 1987.
4. Yurdakök M, Kınık E, Bedük Y, et al. Treatment of enuresis: A study with imipramine, amitriptyline, chlordiazepoxide-clidinium and piracetam. *Turk J Pediatr* 28:171, 1986.
5. Pogady J, Hasko L, Krauss J, Skondia V. Pyrrolidine acetamide in the treatment of enuresis nocturna in pedopsychiatry. *Acta Therapeutica* 3:217, 1977.
6. Axline VM. *Play Therapy* (24th ed). Canada: Houghton Mifflin Co, 1987, pp. 53-128, 171-199.
7. Coleman JC, Broen WE Jr. Psychotherapy. In Coleman JC (ed). *Abnormal Psychology and Modern* Life (4th ed). Illinois: Scott, 1971, pp. 663-691.
8. Schmitt BD. Nocturnal enuresis: an update on treatment. *Pediatr Clin North Am* 29:21, 1982.
9. Shelov SP, Gundy J, Weis JC, et al. Enuresis: a contrast of attitudes of parents and physicians. *Pediatrics* 67:707, 1981.
10. Dimson SB. Toilet training and enuresis. *Br Med J* 2:666, 1959.
11. Jarvelin MR, Vikevain L, Moilanen I, Huttunen NP. Enuresis in seven-year-old children. *Acta Paediatr Scand* 77:148, 1988.
12. Shaffer D, Gardner A, Hedge B. Behavior and bladder disturbances of enuretic children. *Acta Paediatr Scand* 77:148, 1988.
13. Inoue M, Shimojima H, Chiba H, et al. Rhythmic slow-wave observed on nocturnal sleep encephalogram in children with idiopathic nocturnal enuresis. *Sleep* 10:570, 1987.
14. Turton EC, Spear AB. E.E.G. findings in 100 cases of severe enuresis. *Arch Dis Child* 28:316, 1953.
15. Fermaglich JL. Electroencephalographic study of enuretics. *Am J Dis Chid* 118:473, 1969.
16. Gunnarson S, Melin KA. Electroencephalogram in enuresis. *Acta Paediatrica* 40:496, 1951.
17. Poussaint AF, Greenfield R. Epilepsy and enuresis. *Am J Psychiat* 122:1426, 1966.
18. Kaada B, Retvedt A. Enuresis and hyperventilation response in the EEG. *Dev Med Child Neurol* 23:591, 1981.
19. Terho P, Kekomaki M. Management of nocturnal enuresis with vasopressin analogue. *J Urol* 131:925, 1984.
20. Post EM, Richman RA, Blackett PR, et al. Desmopressin response of enuretic children. Effects of age and frequency of enuresis. *Am J Dis Child* 137:962, 1983.
21. Delaere KP, Strijbos WE. Antidiuretic approach with DDAVP for nocturnal enuresis. *Acta Urol Belg* 54:464, 1986.
22. Pedersen PS, Hejl M, Kjøller SS. Desamino-D-arginine vasopressin in childhood nocturnal enuresis. *J Urol* 133:65, 1985.
23. Ferrie BG, MacFarlane J, Glen ES. DDAVP in young enuretic patients: a double-blind trial. *Br J Urol* 56:376, 1984.
24. Young DE, Young RR. Nocturnal enuresis: a review of treatment approaches. *Am Fam Physician* 31:141, 1985.

25. Netly C, Khanna F, McKendry JB, Lovering JS. Effects of different methods of treatment of primary enuresis on psychologic functioning in children. *Can Med Assoc J* 131:577, 1984.

26. Lovering JS, Tallett SE, McKendry JB. Oxybutynin efficacy in the treatment of primary enuresis. *Pediatrics* 81:104, 1988.

27. Van Hoof H. *Nootropil* (4th ed). Brussels: UCB, 1980, pp. 99, 102, 126-127, 187-193.

28. Moffatt ME, Kato C, Pless IB. Improvements in self-concept after treatment of nocturnal enuresis: randomized controlled trial. *J Pediatr* 110:647, 1987.