

TREATMENT OF ENURESIS: A STUDY WITH IMIPRAMINE, AMITRIPTYLINE, CHLORDIAZEPOXIDE-CLIDINIUM AND PIRACETAM*

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Key words: amitriptyline, chlordiazepoxide, clidinium, enuresis, imipramine, piracetam, treatment

The numerous theories concerning the etiology of functional enuresis are matched by the diversity of treatments that have been postulated. These include bladder training with fluid restriction at night, drug therapy and psychotherapy¹⁻⁶. Various drugs have been tried and imipramine has been found to be the most successful drug for the treatment of functional enuresis¹⁻⁶. So a controlled investigation was planned to compare the effectiveness of tricyclic antidepressants (imipramine and amitriptyline), anxiolytic-anticholinergic (chlordiazepoxide-clidinium) and a nootropic drug (piracetam) for enuresis. This paper describes the first investigation in the Turkish series; it was conducted in the busy pediatric outpatients clinic at the social security hospital in Ankara. The usage of piracetam for enuresis in this study is, as far as we know, the second report of its kind in the literature⁷.

Material and Methods

Patients for the study were selected from among the six-year-olds or over, presenting with nocturnal enuresis at the department of pediatrics, who were considered suitable for drug therapy. Patients' age, sex, weight, social class and history of bed-wetting were recorded. A physical examination was carried out. Urine analysis was carried out and bacterial cultures were also taken. Patients with any abnormality in the urine were excluded from the study. Patients who did not come in for control were also excluded.

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Forty-one children were included in the study and of these 14 were put on imipramine, 8 on amitriptyline, 10 on chlordiazepoxide-clidinium and 9 on piracetam. There were 25 boys in the group (61%) and 16 girls (39%). Ages ranged from 6-16 years, the mean being 11. Groups were chosen at random but they were well matched for age and social class.

Prior to the study most of the children had received simple preliminary methods of treatment including wakening the child to go to the toilet at night and fluid restriction.

Thirty-three children (81%) had primary and eight (19%) had secondary enuresis. In many there was a family tendency to enuresis; 21 children (51%) had enuretic brothers or sisters, 15 had a mother or father who had been enuretic as a child, and 10 an aunt or uncle.

The children were randomly assigned to treatment with imipramine, amitriptyline, chlordiazepoxide-clidinium or piracetam for six weeks. The daily dose of the active drug, taken half-an-hour before bedtime, was 25 mg imipramine (Tofranil® 25 mg), 25 mg amitriptyline (Triptilin 25 mg), 5 mg chlordiazepoxide-2.5 mg clidinium bromide (Librax®) or 400 mg piracetam (Nootropil® 800 mg, Nörotrop 400 mg) for the six to 10-years-olds, and the amount was doubled for those aged 11 years and over.

A check list was given to the parents for them to mark off any symptoms that might later be recorded as side effects of the treatment. The children were re-assessed after six weeks of treatment. At this visit each child was examined and the number of wet nights during the six-week period was recorded together with a note on any side-effects. The therapeutic index score was then made, the response to therapy being graded as follows: 0: no improvement, 1: partial improvement and 2: complete cure.

The Kruskal-Wallis analysis was used to compare the four treatments⁸.

Results

The response to therapy with the various drugs is shown in Table I. At the sixth week, a significantly higher therapeutic index score was obtained by the imipramine group than by the others. No significant differences were recorded between the chlordiazepoxide-clidinium and amitriptyline groups and the effectiveness of both drugs was less than that of imipramine. The number of patients cured was significantly less in the piracetam group. No significant side-effects were observed in any groups during therapy.

Discussion

Enuresis is defined as involuntary urination occurring in a child at time when bladder control should have been obtained¹⁻⁵. There is no fixed age for this but by

age five 80% of children are dry at night; 1-2%, however, remain enuretic at ten years^{1-5,9,10}. We do not know the exact incidence of enuresis among Turkish children, but it has been suggested that it may be as high as 21.8% in children around Ankara¹¹. A return of enuresis in a child previously stable always suggests either the occurrence of urinary tract infection (overtly or asymptotically) or else psychological stress at home or at school¹⁻⁵. Children with positive urine cultures and/or any apparent emotional or psychological problems were excluded from this study of the comparative effectiveness of certain drugs.

In enuresis it is postulated that there is a slowness in maturation of urinary continence¹². Very deep sleep and a family history of enuresis are common findings in such patients as was the case in this study¹²⁻¹⁴.

The spontaneous cure rate is high in enuresis because the main factor is delayed maturation. As shown by Forsythe and Redmond¹⁵ in a classical study of 1129 enuretics, the spontaneous cure rate is 14% per annum for patients aged 5-9 years, 16% for patients aged 10-19 years and only 3% were still enuretic at the age of 20 years. The placebo effect of the kind and firm interest of a physician probably cures 30-50% with no other assistance^{6,7,13,15}. Obviously the various drugs are difficult to evaluate since there is such a high rate of spontaneous cure, but since the groups for this study were chosen at random and since the period of treatment was so short in this study – only six weeks in fact – we can safely assume that the role played by spontaneous cure was minimal.

The only medications to have demonstrated a beneficial effect are tricyclic antidepressants which produce a desirable effect in approximately 50 percent of patients, and response usually occurs within one to two weeks^{1-7,16}. Imipramine is one instance of a useful tricyclic antidepressant when 25-50 mg are given at bedtime as in this study. Its effectiveness has also been demonstrated in several double-blind, and placebo-controlled studies^{1-7,16}. As a result imipramine has been recommended for the treatment of enuresis in children over six years of age. Enuresis, however, is a non-specific symptom found in a variety of disorders and despite the effectiveness of imipramine in the management of this symptom, it is recommended that the problem underlying enuresis should be understood and dealt with^{15,17}.

All drugs are potentially dangerous and this is certainly true of the tricyclic antidepressants such as imipramine¹⁸⁻²¹. In this particular study, however, we did not observe any side-effects. It must be remembered, however, that only a small number of patients were being observed, moreover the dose given was low and administered for a short period of time.

Viloxazine, a new non-tricyclic antidepressant, has been found to be a less toxic alternative to imipramine¹. No difference in efficacy has been noted between treatment with imipramine and with viloxazine, but there has been a lower

incidence of unwanted side-effects in patients receiving viloxazine, in particular a lack of anticholinergic effects. Although it has been suggested that the anticholinergic effect of tricyclic antidepressants is responsible for their effectiveness¹, this may not be the case. One anticholinergic drug used in our study, clidinium was found to be less effective than imipramine in the treatment of enuresis.

Piracetam (pyrrolidine acetamide) is representative of the group of so-called nootropic substances which act on the central nervous system. Piracetam increases the activity of the associative brain system, thereby favorably influencing the cerebral functions and it increases cortical control on the subcortical areas. Pogady et al⁷ used piracetam on 37 enuretic children and observed a favorable therapeutic effect. A dose of 400 mg (the same as we used) in the evening, decreased the enuresis frequency by more than 50% in 81% of the responders. The remaining 19% of the responders showed a frequency improvement below 50 percent. In this study piracetam was not found to have any effect on enuresis. In this respect the results of these two studies are contrary to each other, and so new controlled studies, using more patients, are called for to clarify the position.

TABLE I
Some Clinical Features and the Effects of Drugs
Used in the Treatment of Enuretic Children

Group	Drug	No. of patients	Age*	Sex Male : Female	Type Primary : Secondary	Therapeutic index score**
1	Imipramine (Tofranil®)	14	11.2 (7-15)	9 : 5	12 : 2	1.57***
2	Amitriptyline (Triptilin)	8	9.9 (6-16)	4 : 4	5 : 3	1.25
3	Chlordiazepoxide- clidinium (Librax®)	10	12.2 (7-12)	6 : 4	9 : 1	1.30
4	Piracetam (Nootropil® Nörotrop)	9	9.7 (6-14)	6 : 3	7 : 2	0.33

Summary

The effectiveness of the drugs used in the treatment of enuresis on 41 children are evaluated. Imipramine, amitriptyline, chlorthalidone and piracetam were used at random on four different groups. Agreed the groups in all instances were small, but it was shown that 25-50 mg of imipramine administered at bedtime, produced a statistically significant improvement in children with nocturnal enuresis, when compared with the other drugs. Indeed piracetam was found to have no beneficial effect at all.

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