

Comparison of desmopressin and enuresis alarm for nocturnal enuresis

SÖREN WILLE

Open Pediatric Clinic, Falkenberg, Sweden

SUMMARY Fifty children with primary nocturnal enuresis were randomised for a study comparing desmopressin (DDAVP) and enuresis alarm. Forty six completed the trial, 24 of whom were treated with 20 µg intranasal desmopressin nightly and 22 with enuresis alarm for three months. Failures were crossed over and relapses were continued on the same treatment for a further three months. The improvement rate was 70% in the group given desmopressin and 86% in the group treated with alarm; the difference was not significant. During the first week of treatment the group given desmopressin was significantly dryer, and at the end of the study 10 of these patients relapsed compared with one patient in the group given the alarm. No serious side effects were observed.

This study confirms the role of conditioning treatment as preferable in long term treatment of nocturnal enuresis. When this fails or when a safe drug with rapid effect is needed, however, desmopressin is a useful alternative.

Bedwetting among children is a common disorder, affecting 30% at age 4, 10% at age 6, 3% at age 12, and 1% at age 20.¹ Untreated, the spontaneous cure rate is about 15% a year.² Treatment is dominated by two approaches, enuresis alarm and drugs.

The enuresis alarm was invented by Pfaundler in 1904.³ Since then many studies have shown the benefit of these devices,^{3–5} and a recent study comparing different mechanisms showed no important difference in their efficacy.⁶ Treatment usually results in an initial cure in 65–100% of cases with a relapse rate of 9–47%. Modern devices are free of the adverse effects of earlier models such as erythema and ‘buzzer ulcers’.⁷

Treatment with drugs has largely been focused on tricyclic antidepressants especially imipramine or, more recently, antidiuretic agents such as desmopressin (DDAVP). For imipramine the proportion of total remission is 10–50% during treatment and a long term cure in 5–40%.⁸ However, numerous reports of side effects, some lethal, have led to a decline in its use.⁹

Since Dimson in 1977 reported on the effects of desmopressin¹⁰ several double blind, placebo controlled studies have shown the efficacy of the drug often with rapid effect but also often with immediate relapse after ending treatment.^{11–16} The drug seems to be safe with few side effects. As this drug has not

been compared with other treatments for nocturnal enuresis and as no long term studies have been done this study compared the efficacy and safety of desmopressin with an enuresis alarm in a controlled, randomised study of three months’ duration.

Materials and methods

Between January 1982 and August 1983, 87 children with nocturnal enuresis were referred to my office and were screened for entry into the study. Inclusion criteria were: boy or girl older than 6 years; not dry for more than six months after the third year; at least three wet nights a week during observation period; and written, informed parental consent. Exclusion criteria were: treatment for enuresis during previous year; day enuresis; cardiovascular disease; renal disorder; neurological disease; and chronic urinary tract infection.

Of the 56 patients who qualified for randomisation, six chose not to participate. After written and oral information, parental consent was obtained from the remaining 50 patients who were randomised to three months’ treatment with either an enuresis alarm (Eastleigh A1 or A1P with wire mesh pad, N H Eastwood and Son Ltd, London, or Sesam Dry-Bed with aluminium tape plastic pad, Astric Products Ltd, Brighton) or a bedtime dose of 20 µg

desmopressin (Minirin intranasal solution, Ferring Pharmaceuticals, Malmö, Sweden) given by calibrated nasal catheter (Rhinyte). All patients completed a questionnaire. A complete history was taken and physical examination performed. Before and on ending the 3 months' treatment the following laboratory tests were performed: white blood count, sedimentation rate, and serum electrolytes, haemoglobin, and creatinine concentrations. On the same occasions and after four weeks' treatment, a urine sample was taken for culture, density, and osmolality in urine voided at 0500. All patients kept a diary card to note nocturnal events during treatment, including a two week observation period before and at the end of the study. About four weeks after treatment all patients were followed up and all relapses recorded. Patients were instructed to report relapses during the following two months, and these relapses were included in the final result. Patients who did not respond to given treatment were crossed over to the opposite treatment for another three months. Patients who relapsed during the three months after treatment were given the same treatment for a further three months.

Statistical methods. Wilcoxon rank sum test was used to compare the results of individual patients before, during, and after treatment. The outcome of the two groups was compared using the χ^2 test. Student's *t* test was used to compare laboratory values in and between the groups and to compare the mean result of the two groups week for week during treatment.

The study protocol was approved by the Department of Drugs of the National Board of Health and Welfare and the ethical committee of Malmö-Lund University.

Results

Distribution of the social classes of the parents in the two groups was similar.

After the start of the study one girl in the group given desmopressin and one boy in the group given the enuresis alarm withdrew. In the group given the enuresis alarm one girl who developed urinary tract infection and one boy who became dry before he started treatment were excluded, leaving 24 patients in the group given desmopressin and 22 in the group given the alarm.

The enuresis score was calculated from score tables kept at home (dry=1, a little wet=2, very wet=3). Success was defined as less than five wet nights during the last 28 nights (average one wet night or less per week) or significantly lower enuresis score. In this way even patients who were

much more dry than before but still a little wet were counted as clinically significant improvements and therefore as successes. During treatment there was no difference between treatment groups, but due to higher frequency of relapse in the group given desmopressin the result for the group given the alarm was significantly better both during the first two weeks after ($p<0.02$) and three months after treatment ($p<0.001$).

The number of dry nights was analysed week by week during the study. The Figure shows the results. During the first treatment week (week 3) patients treated with desmopressin showed immediate improvement and registered significantly more dry nights than patients in the group given the alarm ($p<0.001$). This trend continued for three weeks. During the last nine weeks the group given the alarm was drier, but this difference was only significant ($p<0.002$) in the 11th week. After treatment both groups were significantly dryer than before, but the group given the enuresis alarm was more so ($p<0.001$ and $p<0.02$ for the group given the alarm and the group given desmopressin against baseline, respectively). The results were not different when analysed according to age or sex.

One patient treated with enuresis alarm relapsed after treatment. New treatment with enuresis alarm

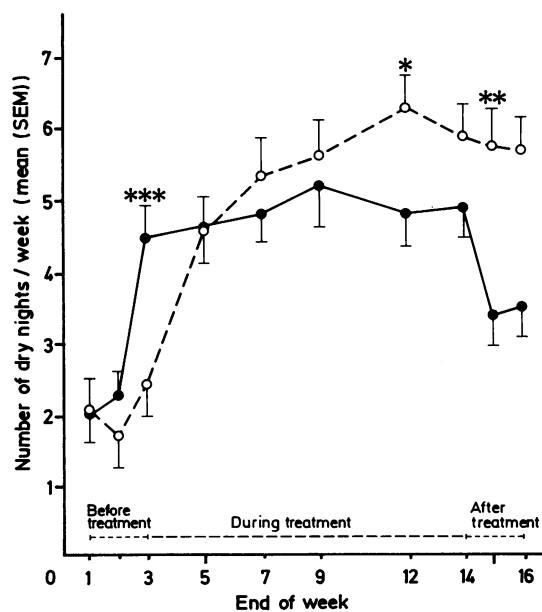


Figure Number of dry nights per week before, during, and after treatment with either desmopressin (●-●; n=24) (* $p<0.05$; ** $p<0.01$; *** $p<0.001$) or enuresis alarm (○-○; n=22).

was without effect. Ten patients who relapsed after treatment with desmopressin were given treatment for a further three months, which proved successful in seven. Four of these patients relapsed immediately after treatment and another within the next two months, leaving two of the 10 patients with a better result after six months' treatment. The number of patients who improved on long term treatment was now 10 (42%) of the group given desmopressin and 18 (82%) of the group given the alarm.

Those who failed to respond to the first treatment regimen were crossed over to the opposite treatment. In the group crossed over from treatment with desmopressin five children did not respond to the alarm, two improved, and by the two month control three were better than before. Of three children who did not respond to the alarm, two improved on treatment with desmopressin, but both relapsed. There was no significant difference between treatment results during or after treatment. One child treated with the alarm dropped out after three weeks owing to no improvement.

There were no significant differences in the results of laboratory tests or blood pressure measurements between or within the groups, except for urine osmolality and density, which were significantly higher during treatment with desmopressin and urine osmolality in the group given the alarm, which was lower during treatment than before. Results of urine cultures and chemical tests were negative in all patients.

No serious adverse effects were registered in any group. In patients treated with desmopressin for three months five (13%) complained of nasal discomfort and one (3%) had occasional nose bleeds. Two patients (5%) experienced a bad taste in the throat. Side effects in the group given the alarm were minor but more frequent; 21 patients (78%) complained of false alarms and five (19%) that the alarm did not work when the child wet the bed. In addition 15 (56%) stated that the alarm did not awake the child and 15 (56%) that other members of the family woke instead. One child was frightened of the alarm.

Discussion

There are only a few controlled studies comparing enuresis alarms with medical treatments. One recent study found alarms to be superior to treatment with imipramine.¹⁷ In this study the success and relapse rates were similar to those of earlier studies of treatment with both alarms and imipramine.⁹

In the present study desmopressin gave better results during the first three weeks, showing that it

has an immediate effect. As in earlier studies most patients relapsed after treatment, but in this study the frequency of wet nights was still significantly lower after treatment compared with before for both groups, although significantly more so for the group given the alarm. In both groups the success rate was superior to the spontaneous cure rate (15% per year), which would have cured less than two patients in each group during the study period.

There has been discussion about how desmopressin works. Birkasova *et al* postulated that the effect was due to the antidiuretic effect of the drug.¹⁴ Aladjem *et al*, however, did not find any rise in morning urine osmolality during treatment,¹² but these measurements were made on urine samples from late morning after the bladder had been emptied of the previous night's urine. In my study parents took urine samples from their children at 0500. In these samples, a significant increase of osmolality of morning urine was found during treatment with desmopressin. These findings support the hypothesis that the effect of desmopressin results from its antidiuretic effect. Surprisingly, in the group given the alarm urine osmolality decreased during the study, a result which may indicate that as the patients became drier their confidence grew so that they relaxed the restriction on their evening liquid intake.

As in other studies using desmopressin the drug did not have any clinically significant adverse effects. In contrast, the reports on adverse effects from treatment with imipramine are common. In a recent review article tricyclic antidepressants were reported to be the commonest cause of fatal poisoning in children.⁹ Older children have died from overdose of imipramine both accidentally and in the belief that a greater dosage gives a better effect. All of this suggests that treatment with tricyclic antidepressants does more harm than good and has no place in the management of childhood enuresis. There is no doubt, however, that treatment with desmopressin offers many benefits. It is safe, has a rapid onset of action, and in about 30% of cases produces lasting improvement after treatment is stopped. I believe that the enuresis alarm is the first choice for treatment, but when this fails or is impracticable and a safe, practical alternative is needed desmopressin is useful.

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Correspondence to Dr S Wille, Open Pediatric Clinic, S-311 01, Falkenberg, Sweden.

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