EVIDENCE AGAINST A SYNERGISTIC EFFECT OF DESMOPRESSIN WITH CONDITIONING IN THE TREATMENT OF NOCTURNAL ENURESIS

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Objective To test the hypothesis that desmopressin facilitates acquisition of continence, we aimed to establish whether, in children with nocturnal enuresis who are desmopressin nonresponders, adjunct desmopressin increases the rate of sustained continence after treatment with a conditioning alarm.

Study design Patients with nocturnal enuresis (n = 358; age range, 6-16 years) completed a 4-week "run-in" course of intranasal desmopressin (20-40 μg). Of these, 207 defined as nonresponders (<50% reduction in wet nights) were randomly assigned to receive either desmopressin (n = 101) or placebo (n = 106) nasal spray, together with conditioning alarm therapy for 8 weeks. Principal outcome measures were remission (28 continuous dry nights) and relapse (>2 wet nights in 2 weeks after having achieved remission).

Results Remission rates were similar in both groups (51.5% desmopressin, 48.1% placebo; 95% CI on difference, −10%, 17%; $P = .63$), and relapse rates were not significantly different (13.5% vs 5.9%; 95% CI on difference, −3.7%, 19%; $P = .19$). Although remission rates were similar, children treated with desmopressin had significantly more dry nights during treatment than those in the placebo group.

Conclusions Desmopressin did not act synergistically with alarm treatment to achieve remission. Therefore, we infer that in partial or nonresponders, desmopressin does not enhance learning. *(J Pediatr 2004;144:351-7)*

Nocturnal enuresis is common.[1] The pathogenesis involves several factors, either separately or in combination: nocturnal polyuria, bladder instability, and failure to arouse to a full bladder.[2,3] A familial predisposition is commonly present.[4] Although there is a high rate of spontaneous remission, the social and emotional consequences are significant and treatment is often desirable.[5] Those children whose symptoms resolve completely have higher self-esteem than those with persistent wetting.[5]

The usual initial treatment of choice in our community is a pad and bell conditioning alarm. This is a proven and safe treatment, but the reported success rate in unselected samples is only 60% to 70%[6] and the relapse rate is ≈30%. The estimate of remission rate (28 consecutive dry nights) is 45% from a systematic overview of published studies taking account of dropouts and relapses.[7] Success requires considerable effort from the child and family over weeks to months.

Intranasal desmopressin (DDAVP, synthetic vasopressin) is an effective treatment for some individuals with enuresis, and the benefit is usually seen within days. The relapse rate on stopping treatment, however, is high (as much as 91%).[8,9] It is speculated that the mechanism is reduction of nocturnal urine volume but central effects could also be involved. Common practice is to use desmopressin for short-term palliative treatment if an alarm has been unsuccessful. Long-term treatment is an alternative and has been shown to be safe.[9] It is associated with a slightly higher remission rate than that which occurs spontaneously (19% compared with ≈15% per year).[8]

There have been conflicting results from studies to date looking at the possible benefits of combination therapy of alarms and desmopressin. Bradbury and Meadow[10] found a 60% better sustained success rate (4 consecutive weeks dry) when 40 μg desmopressin was used with alarm treatment and no increase in the relapse rate. The combination was particularly helpful for children with severe wetting and those with family or behavioral problems. It was hypothesized that the early reduction in wetting achieved

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with desmopressin was helpful in enhancing motivation to continue treatment. This study was not truly randomized and did not include a placebo in the comparison group. Leebeek-Groenwegen et al,[11] in a randomized, placebo-controlled trial of 93 patients, did not find a long-term difference in success between a group given 6 weeks of initial desmopressin with alarm therapy and a placebo group. There was a greater reduction in wet nights in the first 3 weeks in the active group, but the success rates at 6 months were similar, being 36% and 37%. Neither of these studies excluded patients whose enuresis responded to desmopressin alone.

Our hypothesis was that adjunct desmopressin would increase the rate of sustained continence in children treated with a conditioning alarm who had not achieved remission with prior use of desmopressin. By studying the possible benefit in a group of children who did not respond to desmopressin treatment alone, we were looking for synergy between the two treatment modalities. Children who have a complete response to vasopressin are unlikely to derive benefit from alarm therapy as, in the absence of wet nights, learning opportunities will not arise. If the proposed central effects of desmopressin are important, they could enhance learning of the conditioned response.

METHODS

Children with nocturnal enuresis were recruited from the general pediatric outpatient clinic and treated with desmopressin during a run-in period. Subsequently, a double-blinded, randomized, placebo-controlled trial of conditioning alarm therapy with adjunct desmopressin was carried out in the desmopressin nonresponders. The study was approved by the Royal Children's Hospital Ethics in Human Research Committee. Written informed consent was obtained from parents or guardians.

Subjects were eligible to be approached about the trial if they were 6 to 16 years of age and had bed-wetting on at least 2 nights per week in the preceding month. Children were excluded from the study if they had neuropathic bladder, urinary tract abnormalities, cystic fibrosis, allergic rhinitis, urinary tract infection in the preceding 2 weeks, or were concurrently taking imipramine or diuretics. Previous use of an alarm or desmopressin did not exclude entry, and children who also had daytime wetting were included in the study group, but this information was recorded.

The study was carried out between November 1998 and January 2001. Of the 712 subjects who met the inclusion criteria, 344 declined entry, leaving 368 patients enrolled in the study. Baseline data on medical history, family history, previous treatments, and current symptoms were obtained at the initial visit. Baseline diaries recording number of wet nights over a 4-week period before treatment were posted out and collected at the time of enrollment.

In the run-in period, all subjects received 4 weeks of treatment with intranasal desmopressin alone. (Minirin, Ferring AB, Sweden.) The study nurse or physician demonstrated correct administration technique, and written instructions were also supplied. The initial dose was 20 μg, increasing to 40 μg after 2 weeks if there was no response. A response to desmopressin was defined as a ≥50% reduction in the number of wet nights per week on either dose.

Desmopressin responders continued treatment for 3 months with the dose to which they had responded (Fig 1). Treatment was then discontinued, and subjects were followed for a further 2 months. Those subjects who did not respond to intranasal desmopressin were randomly assigned. They began an 8-week treatment with a pad and bell conditioning alarm (Ramsay-Coote, Sandringham, Australia, or Farish-Bissell, Ballarat, Australia) and nasal spray (desmopressin or placebo). The placebo was supplied by Ferring Pharmaceuticals (Ferring AB) and was presented in an identical spray pump. Each was labeled as "study medication" and dispensed randomly by the pharmacist. The study nurse demonstrated the use of the alarm, and the family was also able to view a video describing alarm use. Diaries were kept throughout the study period, recording wet nights and any adverse effects including nasal discomfort and headache. The study nurse, on a 1- to 2-weekly basis, maintained telephone contact with the families. The children were reviewed after the 8-week randomization period and followed-up for 2 months after treatment. All spray pumps were returned at follow-up and weighed by the study nurse, still unaware of the study allocation group, to obtain a measure of treatment compliance.

The primary outcome variables were remission, defined as 28 continuous dry nights after random assignment, and relapse defined as at least 2 wet nights in any 2-week period after having achieved remission.

Comparison of remission and relapse rates was made with the χ^2 test by intention to treat. Subjects who were randomly assigned but for whom data were incomplete remained in the analysis and were assumed to have failed to achieve remission. The change in the mean numbers of dry nights from the start to end of treatment was compared in the two groups by means of the t test. Kaplan-Meier survival analysis was performed by treatment group, with time to remission after random assignment used as failure time. All analyses were carried out with STATA (v. 7, Stata Corp, College Station, Tex).

RESULTS

Those enrolled were not significantly different from those declining participation in terms of baseline characteristics (data not shown). Of those who completed the run-in period, 217 of 358 (61%) were desmopressin nonresponders (Fig 1). The mean age of nonresponders was 9.4 years (SD, 2.08), compared with 8.4 (SD, 1.87) years for desmopressin responders. Of these, 128 (64%) were boys. At enrollment, the mean number of wet nights per 28-night period for the responders was 20.2 (SD, 6.46) and for nonresponders was 23.7 (SD, 5.58). The rates of secondary nocturnal enuresis, family history, previous urinary tract infection, and previous alarm treatment were similar between the groups. Day wetting was associated with a greater risk of nonresponse to

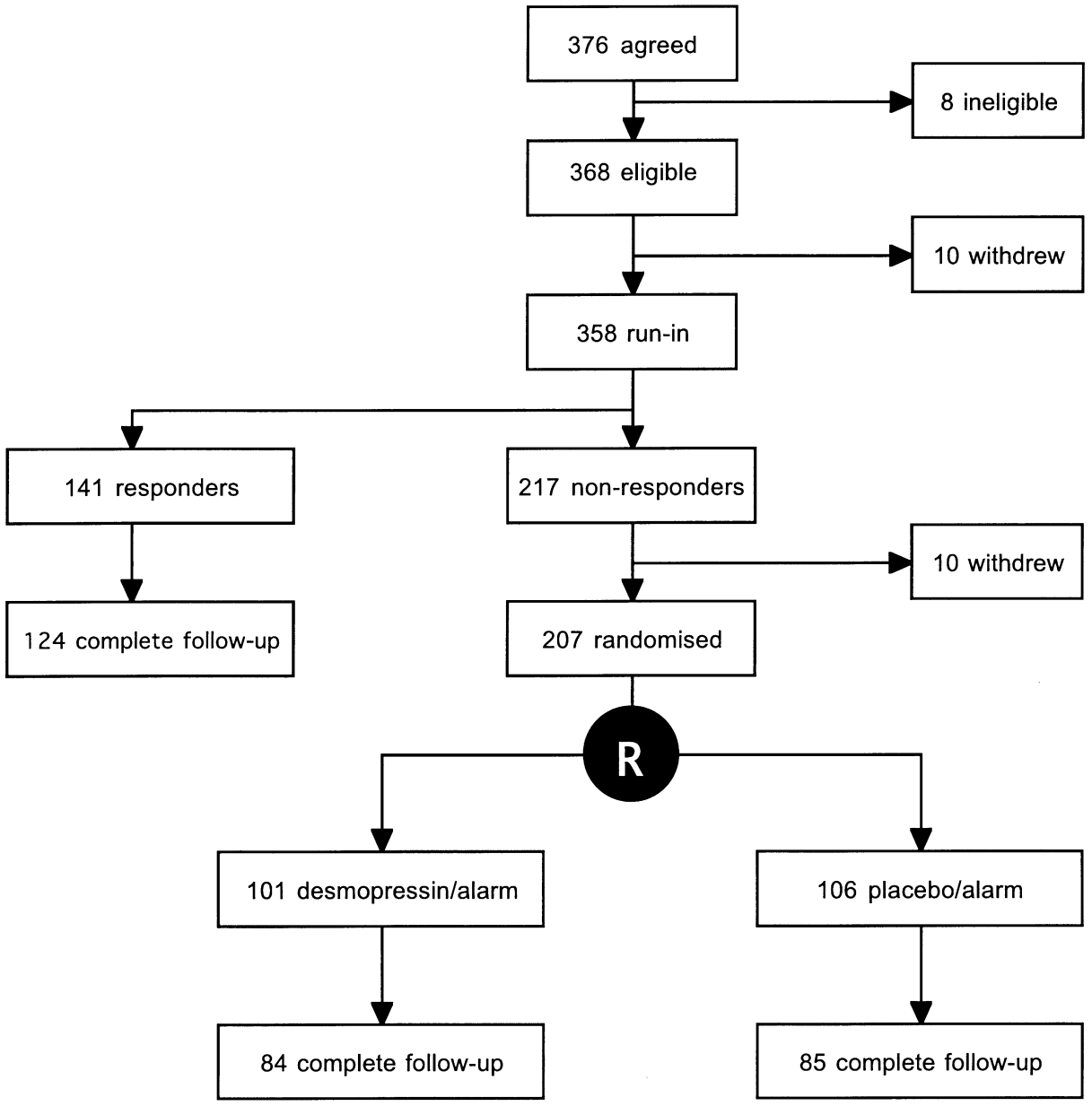

Fig 1. Subject numbers and study design.

desmopressin, with 20 of 28 (71%) daytime wetters being nonresponders.

Of the 358 enrolled, 141 (39%) were responders to desmopressin. Of the responders, 124 continued in the 3-month treatment trial. Fifty-nine subjects (16% of 358, 48% of 124) achieved full remission during treatment. Of these, 23 relapsed during treatment (n = 2), on stopping treatment (n = 17), or within 2 months of stopping treatment (n = 4). There were 36 subjects who did not relapse during the 2-month follow-up period. Therefore, 36 of 358 (10%) subjects had sustained remission from enuresis when treated with desmopressin for 4 months and followed for 2 months after cessation of desmopressin.

The baseline characteristics of the 207 randomly assigned patients are given in Table I. The groups were similar in terms of severity of wetting, age, sex, family history, previous treatment, and coexistence of day wetting.

The rates and reasons for withdrawal from the study or loss to follow-up were similar, with 9 of 101 in the desmopressin group and 17 of 106 in the placebo group. Complete follow-up data (2 months after ceasing treatment) were available for 84 subjects treated with desmopressin and for 85 subjects who had placebo spray.

The rates of remission were similar, with 51.5% in the active group and 48.1% in the placebo group (95% CI on difference, −10%, 17%; $P = .63$) achieving the threshold 28 continuous dry nights after random assignment (Table II). Kaplan-Meier survival analysis revealed that the time to achieve a remission (Fig 2) was similar in both groups and not statistically significantly different (log rank test, $P = .23$).

Table I. Baseline characteristics of randomly assigned subjects

	Desmopressin	Placebo
n	101	106
Male	64 (63%)	78 (73%)
Mean age in years (SD)	8.5 (1.78)	8.3 (1.93)
Mean wet nights in prior 28 at entry (SD)	23.9 (5.05)	23.7 (5.83)
Mean wet nights run-in (SD)	20.9 (5.99)	20.7 (6.35)
Family history positive	45 (45%)	45 (42%)
Secondary enuresis	14 (14%)	9 (8.5%)
Daytime wetting	11 (11%)	8 (7.5%)
Previous treatment		
Alarm	37 (37%)	32 (31%)
Medication	31 (31%)	28 (26%)

In the observation period before enrollment and after the 4-week run-in period of desmopressin treatment, both groups initially had similar numbers of wet nights per week (Table II). After 8 weeks of treatment with alarm and nasal spray, those in the desmopressin group had significantly fewer wet nights per week (mean, 1.8) than those in the placebo-treated group (mean, 2.4; $P < .001$; Fig 3).

The rates of relapse (Table II) were not significantly different, with 7 (13.5%) in the active group and 3 (5.9%) in the placebo group ($P = .19$; 95% CI on difference, −3.7%, 18.9%). The mean time from remission to relapse was 6 weeks in both groups.

Those in the placebo group (24.5%) were more likely than those who received desmopressin (16.8%) to have been prescribed an extension of alarm treatment by their treating physicians, but this difference did not reach significance ($P = .07$).

There were 19 children with concomitant day wetting in the randomized trial. Subgroup analysis and reanalysis with this group excluded did not change the remission rate achieved overall for either arm. Subgroup analysis showed 11 such children in the active arm (6 of 11 achieved remission) and 8 in the placebo arm (3 of 8 achieved remission). If these are removed from the overall group, the remission rates were active, 46 of 90 (51.1%), and placebo, 48 of 98 (49.0%).

Adverse medication effects were uncommon. During the run-in period, there were 7 reports of headache, 7 of nasal congestion, 6 patients with epistaxis, and 1 report each of dizziness and facial rash. One patient with epistaxis and nasal sores withdrew from the study; all others were able to continue treatment without further adverse effects. Of randomly assigned subjects, 2 reported symptoms. One receiving placebo spray had epistaxis and one child receiving desmopressin had headaches. Neither symptom was sufficiently persistent nor severe to necessitate cessation of treatment.

With regard to treatment compliance, complete sets of returned desmopressin or placebo spray pumps were available for 139 of 207 subjects (67%), with 75 subjects allocated to placebo spray, using an average 7.4 grams (SD, 2.27), and 64 subjects allocated desmopressin, using an average 7.3 grams (SD, 2.70) of solution ($P = .76$).

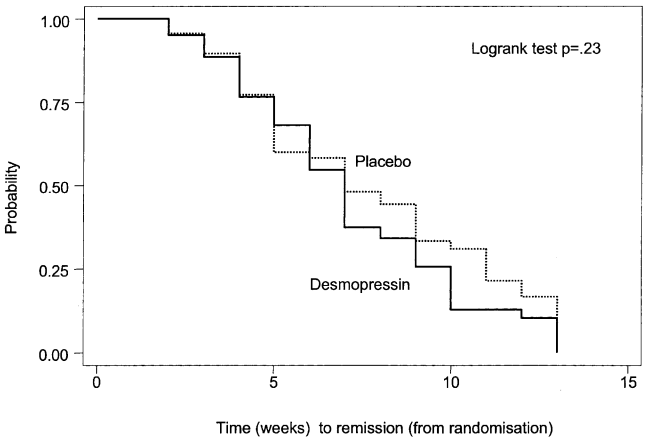

Fig 2. Kaplan-Meier survival estimates by treatment group.

DISCUSSION

In this randomized, placebo-controlled trial, the combination of desmopressin and alarm was not superior to alarm and placebo in terms of the likelihood of achieving remission, with approximately 50% of children in both groups becoming continent. Neither was there any evidence that remission was achieved faster with combination treatment. Adjunct desmopressin had no observed effect on the relapse rate after remission in the first 2 months after treatment. There were significantly more dry nights during treatment when desmopressin was used. This reduction in wet nights and therefore potential learning opportunities with the alarm had no adverse effect on the rate of remission.

Given the potential psychologic and practical advantages of reduced numbers of wet nights, this may be regarded by families and children as a desirable treatment strategy. It may be looked on as having potential benefit for families in whom the burden of frequent nocturnal waking is potentially problematic and may in the past have limited the utility of an alarm. However, because there is no long-term advantage in relation to remission, it is doubtful that it could be recommended as a routine supplement to conditioning therapy.

Our study was different from previous studies of desmopressin and conditioning therapy in that we excluded desmopressin responders to focus on possible synergy between the treatments rather than just additive benefits of combining two treatments that may each have separate benefits. With this difference in mind, however, our findings are in accord with those of the randomized trial conducted by Leebeek-Groenwegen et al.[11] The patient group was similar, but our definition of remission was more stringent. Our results were at variance with those of the Bradbury and Meadow[10] trial. Our group was comparable to that of Bradbury and Meadow, apart from having a higher pretreatment mean number

Table II. Results of randomized trial

		Desmopressin	Placebo	*P* value
n		101	106	
Mean wet nights/week at enrollment (SD)		6.0 (1.27)	5.9 (1.46)	—
	(95 % CI)	(5.71, 6.21)	(5.62, 6.18)	
Mean wet nights end of run-in (SD)		3.7 (4.57)	4.8 (5.91)	.22
	(95 % CI)	(2.75, 4.55)	(3.67, 5.95)	
Mean wet nights end 8-wk treatment period (SD)		1.8 (1.13)	2.4 (1.53)	< .001
	(95 % CI)	(1.55, 1.99)	(2.07, 2.66)	
Change mean number wet nights (SD)		4.3 (2.52)	3.7 (2.70)	.007
	(95 % CI)	(3.81, 4.81)	(3.18, 4.22)	
Remissions		52 (51.5%)	51 (48.1%)	.63
	(95 % CI)	(41%, 62%)	(38%, 58%)	
Relapses at end of 2-mo follow-up		7 (13.5%)	3 (5.9%)	.19
	(95 % CI)	(5.6%, 26%)	(1.2%, 16%)	
Withdrawn or lost to follow-up		9	17	.12
Alarm extension		17	26	.07

of wet nights. Our outcome measures and definitions were equivalent.

The blinding appears to have been successful, with subjects in each group using similar quantities of spray. We found a lower overall response to alarm treatment than has been recorded elsewhere in unselected groups. This probably reflects the severity of the group and because we excluded children who had a favorable response to desmopressin leaving a more treatment-resistant patient group. The sustained remission rate in the desmopressin responders was similar to that reported in the Swedish Enuresis Trial (SWEET).[9]

Butler and Holland[12] have suggested that nocturnal enuresis consists of a number of different conditions with different causes. They argue that alarm treatment is most likely to be effective when arousal problems predominate, and desmopressin most likely to be successful with nocturnal polyuria[12] and that those who fail to respond to desmopressin have an increased likelihood of having bladder instability. Some clinicians would separate children with daytime symptoms and treat them differently.

By selecting desmopressin nonresponders, we studied a group in which reduced bladder capacity[13-15] and detrusor instability[16] were more common. In the Yeung et al[14] study of 41 children with severe primary nocturnal enuresis nonresponsive to desmopressin, all had pathologic cystometrograms during sleep. Watanabe and Azuma[17] found evidence of detrusor instability in one third of patients with monosymptomatic nocturnal enuresis even in the absence of daytime symptoms. This is a group not thought to derive benefit from desmopressin; theoretically it may be of some benefit by keeping urine volumes down, reducing the likelihood of exceeding functional bladder capacity, and by preventing rapid bladder filling, which has been shown to increase detrusor instability. Another possibility is that by reducing nocturnal urine volumes, functional bladder capacity is reached later in the night when arousal is easier. These mechanisms may underlie the reduction in numbers of wet nights observed during combination treatment.

Desmopressin acts on V2 receptors in the renal tubule to increase water reabsorption and thus reduce nocturnal urine volumes. There is evidence that in a subgroup of children with enuresis, there is a lack of circadian rhythm in vasopressin secretion leading to high nocturnal urine production that exceeds bladder capacity.[18] Treatment can thus be thought of as "replacement" therapy. Recently, there has been an interest in the possible central actions of desmopressin. Vasopressin, as well as having a key role in osmoregulation, is a neurotransmitter, exerting its central effects through V1 receptors.[19] Vasopressinergic fibers are mainly found in limbic and hypothalamic structures. Central release of vasopressin possibly has a role in memory, concentration, sleep regulation, and arousal.[20,21] Desmopressin has been found to have V1-b agonist properties.[19]

Central mechanisms may contribute to the effect of desmopressin on enuresis. Eggert (Jonat et al[22]) described a child with nephrogenic diabetes insipidus secondary to a mutation of the V2 receptor gene who became dry on desmopressin treatment. Another mechanism of action apart from a renal effect must have been responsible. Arousal may be enhanced and thus lead to waking to void or inhibition of detrusor contractions during sleep. There is some support for this effect in other work. In the Lackgren et al[23] study, >70% of those who became dry on desmopressin treatment did so by waking to void, suggesting that there may have been an effect on arousal.

There is also some experimental evidence that desmopressin enhances learning. Muller et al[20] have shown an increase in short-term memory in children treated with 20 μg intranasal desmopressin. Beckwith et al[21] showed that DDAVP had beneficial effects on memory and learning in adults. These central effects are interesting but to date remain

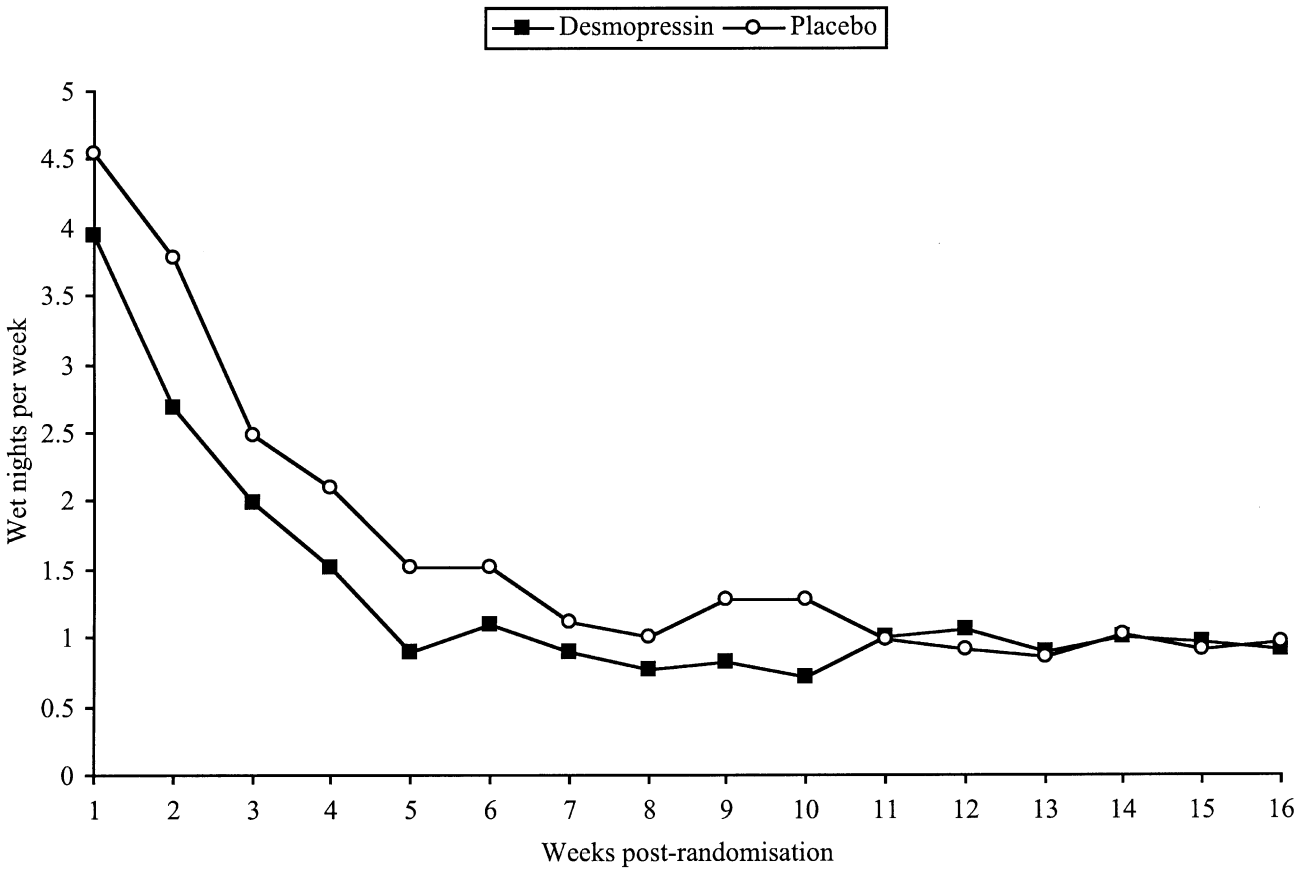

Fig 3. Mean number of wet nights per week.

inconclusive, especially since it has been shown that desmopressin does not cross the blood-brain barrier.[24]

We have not shown an advantage in combining desmopressin with alarm therapy in terms of sustained remission rate. Notwithstanding the fact that our study group included partial and nonresponders, if there had been benefits to learning as the result of a desmopressin central effect, we would have expected an increase in the remission rate or a reduction in relapse rate. It is possible that there was some enhancement of learning but that the reduction in the numbers of wet nights during treatment reduced the learning opportunities so that overall there was no net benefit.

We conclude that adjunct desmopressin does not enhance learning of the conditioned response from pad and bell alarms in nocturnal enuresis in children who are partial or nonresponders. Although there may be an increased number of dry nights during treatment with combined desmopressin and alarm therapy, we cannot recommend this as a routine strategy.

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REFERENCES

1. Bower WF, Moore KH, Shepherd RB, Adams RD. The epidemiology of childhood enuresis in Australia. Br J Urol 1996;78:602-6.

2. Watanabe H. Sleep patterns in children with nocturnal enuresis. Scand J Urol Nephrol 1995;173(suppl):37-42.

3. Wolfish NM, Pivik RT, Busby KA. Elevated sleep arousal thresholds in enuretic boys: clinical implications. Acta Paediatr 1997;86:381-4.

4. Schaumburg HL, Rittig S, Djurhuus JC. No relationship between family history of enuresis and response to desmopressin. J Urol 2001; 166:2435-7.

5. Hagglof B, Andren O, Bergstrom E, Marklund L, Wendelius M. Self esteem before and after treatment in children with nocturnal enuresis and urinary incontinence. Scan J Urol Nephrol 1996;183(suppl):79-82.

6. Forsyth WI, Butler RJ. Fifty years of enuresis alarms. Arch Dis Child 1989;64:879-88.

7. Kristenson G, Jensen IN. Meta-analyses of results of alarm treatment for nocturnal enuresis reporting practice, criteria and frequency of bed wetting. Scand J Urol Nephrol 2003;37:232-8.

8. Riccabona M, Oswald J, Galuninger P. Long term use and tapered dose reduction of intranasal desmopressin in the treatment of 155 enuretic children. Br J Urol 1998;81(suppl):26-8.

9. Tullus K, Bergstrom R, Fosdal I, Winnergard I, Hjalmas K. Efficacy and safety during long-term treatment of primary monosymptomatic nocturnal enuresis with desmopressin. Acta Paediatr 1999;88:1274-8.

10. Bradbury MG, Meadow SR. Combined treatment with enuresis alarm and desmopressin for nocturnal enuresis. Acta Paediatr 1995;84:1014-8.

11. Leebeek-Groenwegen A, Blom J, Sukhai R, Van der Heijden B. Efficacy of desmopressin combined with alarm therapy for monosymptomatic nocturnal enuresis. J Urol 2001;166:2456-8.

12. Butler RJ, Holland P. The three systems: a conceptual way of understanding nocturnal enuresis. Scand J Urol Nephrol 2000;34:270-7.

13. Neveus T, Lackgren G, Tuvemo T, Hetta J, Hjalmas K, Stenberg A. Enuresis: background and treatment. Scand J Urol Nephrol 2000; 206(suppl):1-44.
14. Yeung CK, Chiu HN, Sit FK. Bladder dysfunction in children with refractory monsymptomatic primary nocturnal enuresis. J Urol 1999;162: 1049-1055.
15. Hamano S, Yamanishi T, Igarashi T, Ito H, Murakami S. Functional bladder capacity as a predictor of response to desmopressin and retention control training in monosymptomatic nocturnal enuresis. Eur J Urol 2000; 37:718-22.
16. Neveus T, Tuvemo T, Lackgren G, Stenberg A. Bladder capacity and renal concentrating ability in enuresis: pathogenic implications. J Urol 2001; 165:2022-5.
17. Watanabe H, Azuma Y. A proposal for a classification system of nocturnal enuresis based on overnight simultaneous monitoring of electroencephalography and cystometry. Sleep 1989;12:257-64.
18. Devitt H, Holland P, Butler RJ, Redfern E, Hiley E, Roberts G. Plasma vasopressin and response to treatment in primary nocturnal enuresis. Arch Dis Child 1999;80:448-51.
19. Saito M, Tahara A, Sugimoto T. 1-Desamino-8-D-arginine vasopressin (DDAVP) as an agonist on V1-b vasopressin receptor. Biochem Pharmacol 1997;53:1711-7.
20. Muller D, Florkowski H, Chavez-Kattau K, Carlsson G, Eggert P. The effect of desmopressin on short-term memory in children with primary nocturnal enuresis. J Urol 2001;166:2432-4.
21. Beckwith BE, Petros T, Bergloff PJ, Staebler RJ. Vasopressin analog (DDAVP) facilitates recall of narrative prose. Behav Neurosci 1987;101: 429-32.
22. Jonat S, Santer R, Schneppenheim R, Obser T, Eggert P. Effect of DDAVP on nocturnal enuresis in a patient with nephrogenic diabetes insipidus. Arch Dis Child 1999;81:57-9.
23. Lackgren G, Lilja B, Neveus T, Stenberg A. Desmopressin in the treatment of severe nocturnal enuresis: a 7-year follow-up study. Br J Urol 1998;81:17-23.
24. Soelberg SP, Vilhardt H, Gjerris F, Warberg J. Impermeability of the blood-cerebrospinal fluid barrier to DDAVP in patients with acquired communicating hydrocephalus. Eur J Clin Invest 1984;14: 435-9.

50 Years Ago in *The Journal of Pediatrics*

THE TREATMENT OF ERYTHROBLASTOSIS FETALIS WITH REPLACEMENT TRANSFUSION

Feldman F, Lichtmen HC, Ginsberg V. J Pediatr 1954;44:181-90

Fifty years ago, erythroblastosis fetalis most frequently occurred after a mother whose red blood cells did not contain the D antigen of the Rh group was sensitized by a pregnancy in which the fetus was Rh (D)-positive. In subsequent pregnancies with an Rh-positive fetus, the maternal anti-Rh IgG would cross the placenta and cause hemolysis of the fetal red blood cells with resultant anemia and erythroblastosis. The immaturity of glucuronyl transferase in the fetus and newborn led to accumulation of very high levels of bilirubin, which would cross the blood-brain barrier, often producing kernicterus. Substantial morbidity and mortality occurred.

Exchange transfusion allowed effective treatment of anemic infants and those with rapidly rising serum bilirubin concentrations, as long as the situation was recognized promptly and treatment begun immediately. In this article, the authors describe their experience with 106 cases treated with exchange transfusion. The mortality rate they describe with exchange transfusion was 6.6%, a significant improvement over previous experience, but about 20 times higher than that seen today. Patient selection and the state of neonatal intensive care were undoubtedly factors in the high mortality; the technical aspects of exchange transfusion had not yet been refined. An initial withdrawal of 50 mL of blood from a newborn, for example, was performed to enhance the efficiency of the exchange procedure, but would be viewed as too physiologically stressful today.

Fortunately, preventive care and prenatal diagnosis have improved the outcome for this disease. There remains a small, but important role for exchange transfusion in this and several other diseases.

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