Low-Dose DDAVP in Nocturnal Enuresis

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Summary: A five-year experience with the vasopressin analogue desmopressin acetate (DDAVP) for nocturnal enuresis is described in 59 children. The initial starting dose of 5 μg at bedtime is lower than that reported in other series. Eighty-one percent of patients required 10 μg or less to achieve improvement or resolution of bedwetting.

Introduction

Children throughout history have been distressed by nocturnal enuresis, and physicians have been frustrated in their search for the ideal treatment. Glicklich[1] described the trials and tolls of bedwetting in the 19th century; frequent changes of linen were impossible for poor families and household friction led to ill treatment, whereas bedwetting children of high social station were ineligible for boarding schools. Treatments available in that era included belladonna, preparations of arsenic and steel, and injection of ergot into the ischiorectal fossa.

The point at which nocturnal enuresis can fairly be described as a disease varies according to family, patient, and social situation. The prevalence of nocturnal enuresis in six-year-olds is estimated at 13%, decreasing to 7% by age eight.[2] In the younger children it is difficult to believe that bedwetting should engender serious medical attention since left untreated, the spontaneous cure rate by age 14 is 98% to 99%.[3] However, by eight to ten years of age, nocturnal enuresis has significant costs in terms of self-esteem, inconvenience, and peer standing.

Current treatments include bladder-retention training, psychotherapy, motivational therapy, behavioral modification, and pharmacologic intervention. Desmopressin acetate (DDAVP), a recent addition to the pharmacologic armamentarium, is a synthetic analogue of human arginine vasopressin (ADH). Dimson reported its use in children with enuresis in 1977, and subsequent experience has established its efficacy and safety at dosages of 20 to 40 μg intranasally at bedtime.[4-6]

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Material and Methods

DDAVP was used in 59 patients with nocturnal enuresis over a five-year period. Forty boys and 19 girls, 8 to 20 years of age, with a mean of 12.5 years, made up the study group. History, physical examination, blood pressure, urinalysis, and urine specific gravity at the initiation of treatment were normal for each patient. Patients with such factors as excessive fluid intake, extraordinary headaches, or cystic fibrosis were excluded. Forty-seven patients were otherwise healthy children and 12 had associated medical problems consisting of vesicoureteral reflux, growth hormone deficiency, seizure disorder, factor IX deficiency, undescended testicle, hypertension, testicular torsion, proteinuria, encopresis and mental retardation. Fifty-one percent of patients had received previous forms of treatment consisting of anticholinergics (17%), imipramine (57%), and moisture-sensing alarms (26%).

The initial starting dose of DDAVP was 5 μg intranasally at bedtime. If the initial 5 μg dose was unsuccessful after two weeks, it was increased to 10 μg. Instructions and demonstration for use were given by a nurse clinician. Patients were requested to withhold intake of fluids an hour before bedtime.

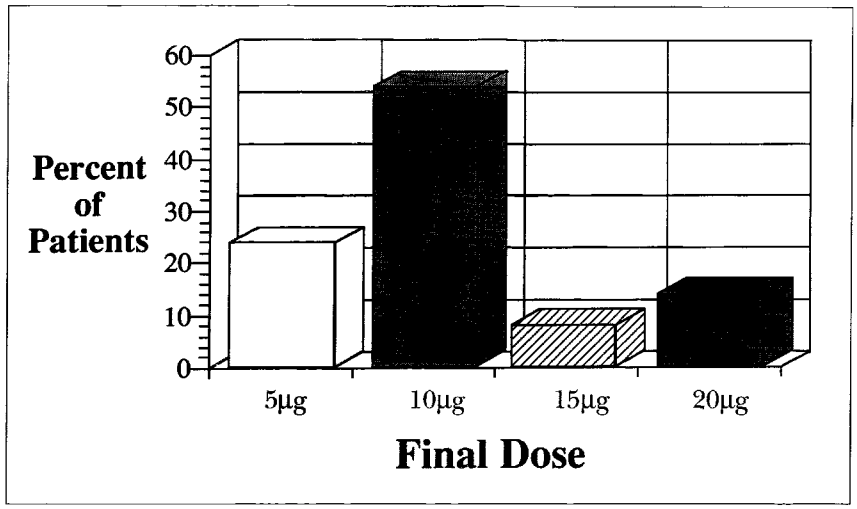

Figure 1. Final dose of DDAVP.

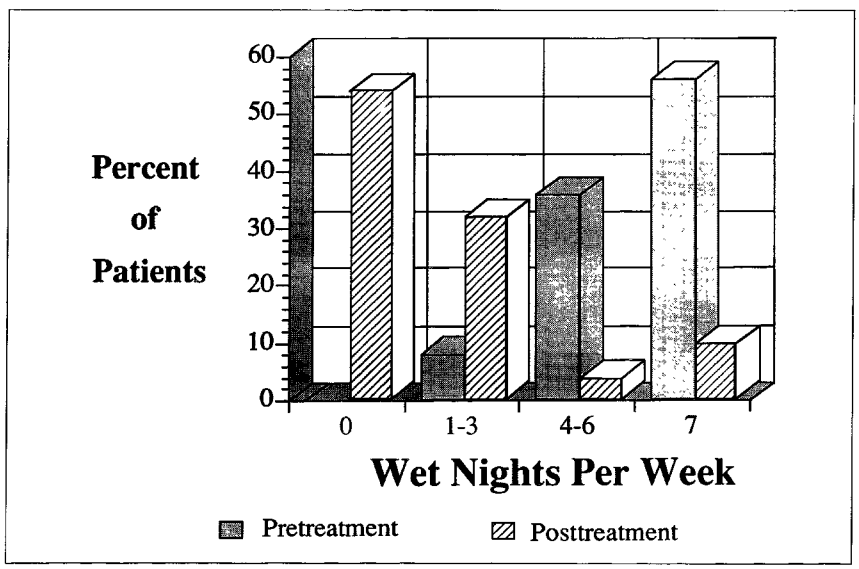

Figure 2. Wet nights per week pre- and posttreatment.

To administer the medication, the nose was cleared of secretions and debris, the medication was dispensed to the proper dose level, the delivery tube was placed just inside the nose, and the dose was briskly inhaled. The metered dose nasal inhaler operated similarly. The medicine is refrigerated between applications. Morning electrolytes were checked three days after initiation of therapy. Patients or parents kept a diary of the wet and dry nights. During this time there were no other limitations of fluid intake. Follow-up and dosage increases were performed at clinic visits and by telephone. After the child maintained nighttme dryness for six to 12 months, the families were encouraged to decrease the doses and frequency of administration of the DDAVP. A satisfactory result was defined as complete nighttime dryness or a decrease in the number of recorded wet nights.

Results

Dose levels of 10 μg or less produced satisfactory results in 81% of patients (Figure 1). During treatment, 54% of the children achieved dryness every night and 38% had a decrease in the number of wet nights per week (Figure 2). No one relapsed on treatment after reaching an effective dose. Only 8% of the patients had no improvement on DDAVP. At the present time, 52 patients are still taking DDAVP, four relapsed when taken off medication, and three are completely dry since being taken off DDAVP. The range of serum sodium concentrations was 130 to 140 mEq/L, with a mean of 138 mEq/L. The only complication was nasal mucosa dryness and headaches in a single patient after beginning DDAVP.

The cost at our hospital was $2.11 per 10-μg dose (0.1 mL) for the 2.5-mL bottle preparation, or $1.67 per 10-μg dose of the spray. The monthly cost (30 nights) of a 5-μg/night course with the liquid was $31.80, whereas the monthly cost of a 20-μg/night course with the spray was $100.20.

Discussion

Nocturnal enuresis is multifactorial in etiology. Contributing factors include psychogenic problems, stress, delayed maturation, allergy, polydipsia, urinary tract infections, diabetes insipidus, diabetes mellitus, and pinworms. In 1952, Poulton[7] suggested increased nocturnal production of urine as a factor in enuresis. Norgaard et al[8] identified nocturnal polyuria and abnormal secretion patterns of antidiuretic hormone secretion in nocturnal enuretics. That study revealed a failure of the normal nocturnal in-

crease in ADH and thereby implicated nocturnal polyuria as a bedwetting factor. The assumption is that nocturnal urine volume exceeds functional bladder capacity and triggers a voiding contraction. The higher nocturnal output of urine is not, by itself, a sufficient explanation for nocturnal enuresis; these patients also must have a failure in being awakened by their full bladders. For this reason, concomitant use of an alarm is logical,[9] although this was not done in our series. In 1975, George et al[10] demonstrated a normal circadian ADH variation in adult men. Rittig et al[11] discerned a similar ADH rhythmicity in normal adolescents, an absence of that variation in enuretic adolescents, and an increase in the nocturnal urine output along with a lower osmolality in adolescents with enuresis when compared with normal adolescents. Secretion patterns of ADH have not been studied in younger patients with nocturnal enuresis. Although we found good responses during treatment, our relapse rate was similar to that reported by others.[12] Many patients are so satisfied with DDAVP that they are reluctant to stop the medication and thus we have not yet been able to define a true relapse rate. We have not tapered the dose as suggested by some authors.[13]

Every bedwetting treatment has its own drawbacks, in addition to incomplete efficacy. For siblings who must share a bedroom, the alarm is an unhappy choice. Tofranil can be associated with behavioral changes and has a narrow safety-to-lethal dose gap.[14]

Anticholinergics can cause flushing, dryness, and behavioral changes. Behavioral therapy is not an easily identifiable treatment for most practitioners. DDAVP is effective in the substantial subgroup of patients with nocturnal enuresis with abnormal ADH secretion patterns. The side effects of DDAVP appear to be few, but real.[5,15,16]

Our results with DDAVP are not significantly different than those reported for use of an alarm, although our experience with alarms falls short of published success rates.[17,18] We have used small doses of DDAVP with results similar to those obtained with larger doses. The drug is expensive, and for that reason alone the least amount necessary should be useful. On the other hand, the spray application, which delivers a minimum of 10 μg (0.1 mL) requires much less patient instruction and is less expensive per microgram than the liquid. Although the costs of medication may be daunting, one must consider the costs of diapers, extra laundry, and ruined mattresses to place DDAVP in appropriate context. Even in lower doses than recommended, DDAVP is an effective and satisfactory alternative to other forms of treatment of nocturnal enuresis in children eight years of age and older.

REFERENCES

1. Glicklich LB. An historical account of enuresis. *Pediatrics.* 1951;8:859-876.
2. Fergusson DM, Horwood LJ, Shannon FT. Factors related to the age of attainment of nocturnal bladder control: an eight-year longitudinal study. *Pediatrics.* 1986;78:884-890.
3. Foxman B, Valdez RB, Brook RH. Childhood enuresis: prevalence, perceived impact and prescribed treatments. *Pediatrics.* 1986;77:482-487.
4. Dimson SB. Desmopressin as a treatment for enuresis. *Lancet.* 1977;1:1260.
5. Klauber GT. Clinical efficacy and safety of desmopressin in the treatment of nocturnal enuresis. *J Pediatr.* 1989;114:(4,Pt.2)719-722.
6. Pederson PS, Hejl M, Kjoller SS. Desamino-d-arginine vasopressin in childhood nocturnal enuresis. J Urol. 1985;133:65-66.
7. Poulton EM. Relative nocturnal polyuria as a factor in enuresis. *Lancet.* 1952;2:906.
8. Norgaard JP, Pedersen EB, Djurhuus JC. Diurnal anti-diuretic hormone levels in enuretics. *J Urol.* 1985;134:1029-1031.
9. Sukhai RN, Mol J, Harris AS. Combined therapy of enuresis alarm and desmopressin in the treatment of nocturnal enuresis. Eur J Pediatr. 1989;148:465-467.
10. George PL, Messerli FH, Genest J, et al. Diurnal variation of plasma vasopressin in man. *J Clin Endocrinol Metab.* 1975;41:332-338.
11. Rittig S, Knudsen UB, Norgaard JP, et al. Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. Am J Physiol. 1989;256:664-671.
12. Post EM, Richman RA, Blackett PR, et al. Desmopressin response of enuretic children. Effects of age and frequency of enuresis. *Am J Dis Child.* 1983;137:962-963.
13. Miller K. Goldberg S, Atkin B. Nocturnal enuresis: experience with long-term use of intranasally administered desmopressin. Pediatr. 1989;114:723-726.
14. Palmisano PA. Enuresis: causes, cures and cautions. West J Med. 1976;125:347-349.
15. Simmonds EJ, Mahony MJ, Littlewood JM. Convulsion and coma after intranasal desmopressin in cystic fibrosis. Br Med J. 1988;297:1614.
16. Salvatoni A, Maghnie M, Lorini R, et al. Hyponatremia and seizures during desmopressin acetate treatment in hypothyroidism. J Pediatr. 1990;116:835-836.
17. Kass EJ, Diokno AC, Montealegre A. Enuresis: principles of management and results of treatment. J Urol. 1979;121:794-796.
18. Wille S. Comparison of desmopressin and enuresis alarm for nocturnal enuresis. Arch Dis Child. 1986;61:30-33.