

Title: Variability in Oral DDAVP Dose Requirements in Children with Central Diabetes Insipidus.

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Abstract:

There is tremendous inconsistency in the amount of oral desmopressin (DDAVP) that children with central diabetes insipidus (CDI) require. We investigated whether clinical characteristics influenced DDAVP dose requirements in 100 children with CDI. Extremely large doses were associated with acquired etiology ($P=0.04$), higher BMI z-score, intact thirst and additional pituitary hormone deficiencies ($P < 0.001$).

Introduction

Central diabetes insipidus (CDI) is a complex disorder that results from a deficiency of arginine vasopressin (AVP)[1]. It manifests clinically as polyuria and polydipsia due to an inability to conserve free water and the diagnosis is confirmed by the finding of an inappropriately dilute urine in the setting of an elevated serum osmolality [2]. CDI may be congenital or acquired and has an estimated prevalence of 1 in 25,000 individuals [3]. Congenital causes include developmental or structural abnormalities of the hypothalamus or pituitary gland as well as genetic mutations that are typically inherited in an autosomal dominant or autosomal recessive fashion [4]. Damage to or destruction of the neurohypophysis form the basis for acquired cases, and include infections, trauma, surgery, neoplasms and infiltrative processes such as Langerhans cell histiocytosis [5].

The cornerstones of the treatment of CDI are desmopressin (DDAVP) and free access to water. Although multiple routes of administration exist, oral DDAVP is the preferred formulation in children due to the simplicity of administration, easy dose titration, low risk of hyponatremia and lack of necessity of refrigeration. However, the daily oral DDAVP requirement varies tremendously, with some children needing ≥ 100 -fold higher doses than others. It is unknown whether individual clinical characteristics such as the presence of an intact thirst mechanism, etiology of CDI, or multiple pituitary hormone deficiencies are associated with DDAVP dose requirements. Our goal was to systematically examine treatment regimens in a cohort of children with CDI and determine whether there are clinical factors or demographic characteristics that might influence DDAVP dose requirements. Specifically, we aimed to compare patients who required inordinately high doses of DDAVP with those on more traditional dose schedules.

Methods

After institutional review board approval, medical records of children with CDI followed in the pediatric endocrine clinic at Riley Hospital for Children were reviewed. Inclusion criteria included all children ≤ 18 years of age diagnosed with CDI treated with oral DDAVP. Variables analyzed included sex, age at diagnosis, ethnicity, DDAVP dosage, etiology of CDI, BMI z score, presence of intact thirst, family history of CDI and presence of additional pituitary hormone deficiencies. Based on published typical dose ranges of 0.2-0.6 mg daily for oral DDAVP [6], we arbitrarily considered a large dose to be ≥ 1.00 mg/day and a normal dose to be ≤ 1.00 mg/day. Categorical variables were analyzed using frequencies and proportions and compared using χ^2 tests. Continuous variables were expressed using mean \pm standard deviation (SD) and compared using the Student t test. A two-sided P value < 0.05 was considered statistically significant for all analyses except for one in which a left sided P value < 0.05 was considered significant. This is indicated by an asterisk in Table 1. Data were analyzed using the statistical software SPSS version 27.0.

Results

A total of 100 patients with CDI treated with oral DDAVP were identified. The mean age at diagnosis was 7.5 ± 0.6 years and 84% were boys. An intact thirst was present in 75% of patients. Congenital etiologies including genetic mutations and structural brain abnormalities were present in 35%. The most common structural anomalies were septo-optic dysplasia and holoprosencephaly. Of the 65 patients with acquired causes, the most common were brain tumors which occurred in 38%. Just over half of patients with acquired CDI had additional pituitary hormone deficiencies. The range of daily DDAVP doses was 0.04 to 10 mg with a mean of 0.92

+1.62. Patients with acquired CDI were on a higher average dose than those with congenital etiologies, (1.087 ± 1.91 mg vs 0.6 ± 0.13 mg, $P= 0.032^*$). A large dose requirement was present in 19% of patients who were receiving 3.1 ± 2.8 mg daily compared with a dose of 0.38 ± 0.2 mg in the remaining 81%, $p < 0.0001$. Baseline characteristics are summarized in Table I. Among patients who required large doses, 84% had CDI due to an acquired etiology compared with 15.8% who had a congenital cause, $p = 0.042$. The mean BMI z score was higher among patients who required large doses than those who did not, 1.3 ± 1.0 vs 0.6 ± 1.2 , $p = 0.027$, and an intact thirst mechanism was more likely to be present (94% vs 71.3%, $p < 0.0001$). Additional pituitary hormone deficiencies were also more common in the large dose group (84% vs 75%, $P < 0.0001$). No correlation was seen between DDAVP dose and age or BMI. These results are seen in Table 2.

Discussion

In this study, we examined DDAVP dose requirements in a cohort of children with CDI followed at a single institution. As has been previously reported, intracranial tumors are the most common cause of acquired CDI and a subset of children with DI do not have an intact thirst [7, 8].

Children with adipsic DI are notoriously difficult to manage due to the wide swings in serum sodium that invariably occur [9]. Interestingly, the children lacking an intact thirst mechanism in our study were less likely to require large doses of DDAVP, perhaps because their daily fluid volume was kept constant at a maintenance level. That children with acquired DI, which often results from some form of CNS insult, and those with multiple pituitary hormone deficiencies were more likely to require large doses, suggests that they may have had a more severe form of the condition than those requiring less DDAVP. While some patients are felt to have an “altered set point” for secretion of AVP by the hypothalamic supraoptic and paraventricular nuclei [10],

all of the children in our study unequivocally met criteria for DI. Alternative explanations for a large dose requirement in some children would include differences in absorption and/or metabolism of DDAVP. While poor compliance is always a possibility, no concerns were noted regarding adherence to treatment in the medical records of patients requiring higher DDAVP doses.

When a diagnosis of CDI is made, the initial dose of DDAVP that is prescribed is empiric, and is based on clinical experience and an “educated guess” of what a particular patient might require. Parents are instructed to watch for “break-through” in the form of increased thirst and urination, prior to giving the next dose of DDAVP [11]. The goals of treatment are to achieve normal salt and water balance so as to allow children to sleep through the night and get through the school day without the disruption of frequent bathroom breaks.

We arbitrarily considered a large dose of DDAVP to be more than or equal to 1.0 mg/day. Clinical characteristics associated with large dose requirements were acquired etiology of CDI, a higher BMI z-score, intact thirst and presence of additional pituitary hormone deficiencies. As long as the serum sodium is within the goal range, there is no absolute maximum amount of DDAVP that may be prescribed, and the dose can be titrated upward as needed to control symptoms. Beyond the observation that some children require extremely large amounts of DDAVP, the particularly wide dosage range of 0.04 mg to 10 mg daily among children in our study is striking.

Limitations of our study include the retrospective design and that information in the medical records may be missing or incomplete. However, to our knowledge, ours is the first study to investigate the variability in DDAVP dose requirements in children with CDI, and to examine its relationship to clinical characteristics.

Our findings provide useful prognostic information for providers caring for children diagnosed with CDI.

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