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RESPONSE TO ORAL DDAVP FOR NOCTURIA IN OLDER MEN: RELATION TO RENAL CONCENTRATING CAPACITY AND ARGININE VASOPRESSIN DEFICIENCY

Hypothesis / aims of study

We sought to determine the maximal renal concentrating capacity and prevalence of arginine vasopressin (AVP) deficiency, as defined by standardized water deprivation testing, in a sample of older men with nocturia and no evidence of bladder outlet obstruction and whether these abnormalities predicted responsiveness to oral ddAVP treatment.

Study design, materials and methods

Design: Clinical Research Center evaluation of men with nocturia followed by a randomized, double-blinded, placebo-controlled, dosage titrated, cross-over study (RCT) of oral ddAVP.

Setting and Participants: Male subjects were recruited between 1999-2002 if they were over 65 years of age, enrolled for primary care at the Medical Center, and had no evidence of bladder outlet obstruction. Subjects underwent a detailed history, physical, and laboratory studies to exclude potentially treatable causes of nocturia. All study procedures were approved by the local Institutional Review Board and Research Committee. Those with a maximum urinary flow rate of <10 ml/sec underwent a pressure-flow study to exclude a diagnosis of bladder outlet obstruction. Subjects then underwent a 2-day stay at the General Clinical Research Center, which included an overnight water deprivation study.

Intervention: For the RCT, each participant was started on 0.2 mg of either ddAVP or placebo, titrated up to 0.4 mg if the serum sodium was greater than 130 mEq/L and nocturia persisted, or titrated down to 0.1 mg if the serum sodium was below 130 mEq/L. Following 7 days of treatment at the optimum dosage, participants had a one week washout and then were crossed over to the opposite intervention.

Measurements: Effect on nocturia was determined by self-reports of nocturia and also by diary recordings (3 day recordings on the final days of the 7 day treatment) of voids that occurred following going to bed time and prior to awakening. Participants also recorded the time and volume of their voids (in both mL and in gram weight using a dietary scale). Responsiveness to ddAVP was defined a priori as a 50% or greater reduction in baseline nocturia episodes. Nocturnal urine volume and % of urine excreted at night were also examined. Statistical analysis was performed using SPSS version 12.

Results

Fourteen individuals completed all visits of the protocol. Their demographic and baseline information is shown in Table 1. Two of the 14 participants met criteria for AVP deficiency by water deprivation testing.

All participants were titrated to a final dosage of 0.4 mg of the placebo. Nine participants were titrated to 0.4 mg of ddAVP, 3 remained on 0.2 mg, and 2 were titrated downward to 0.1 mg. Of the five participants whose final dosage was less than 0.4 mg, two developed hyponatremia, one had weight gain, one had dizziness, and one had resolution of nocturia on the 0.2 mg dosage. Two of the five participants titrated up to the 0.4 mg dosage developed hyponatremia. All hyponatremia resolved with ddAVP discontinuation.

There was no time ordering effect of the results; it did not matter whether participants were randomized to placebo or active drug first. Results of the treatment trial are summarized in Table 2. Four of the 14 participants on ddAVP had a 50% or greater reduction in nocturia, and 5 of the 14 patients on placebo had a 50% or greater reduction while on placebo. For the group, ddAVP treatment resulted in a significant decrease in nocturnal urine volume and number of episodes of nocturia. There was no statistical association between maximum urine osmolality, water deprivation status, or baseline nocturnal polyuria and reduction in either nocturia or nocturnal urine volume. Those individuals titrated downwards

to a final dosage of 0.1 mg had a statistically significant greater reduction in nocturia when compared to those on a final dose of either 0.2 or 0.4 mg.

Interpretation of results

In this small sample of 14 older men, oral ddAVP resulted in significant reductions in nocturia and night urine volume when compared to baseline. However, the effect on nocturia was not statistically different from the effect of placebo. There was no relationship between maximum urine osmolality achieved by water deprivation and aqueous vasopressin and reduction in nocturia from oral ddAVP.

Concluding message

This trial differed from larger trials of oral ddAVP in that participants were older and had a blinded titration of ddAVP, as opposed to an open-label run in. While these patients had a less robust reduction in nocturia compared to other clinical trials, they did have a physiological response to the drug as reflected by decrease in nocturnal urine volume. That four of 14 (28.5%) participants had hyponatremia is consistent with other studies showing a higher rate of hyponatremia in older individuals; this may also be an effect of the titration algorithm. Too few participants who completed the protocol had abnormal water deprivation tests, which limited the ability to fully investigate this research aim.

Table 1: Descriptive Statistics and Baseline Characteristics of 14 participants

	Mean	**Range**
Age (mean, range)	73.9 years	67-80
Urine excreted during sleeping hours as a percentage of total 24 hour output	46.2%	27-74%
Baseline serum sodium	139 mEq/dL	134-142
Maximum flow rate (Qmax)	15.6 mL/sec	9-29.5 mL/sec
Post void residual (measured by ultrasound)	61 mL	10-269 mL
Maximum urine osmolality following water deprivation and/or aqueous vasopressin	646 mOsm	432-830 mOsm
	Frequency	**Percentage**
Nocturia self-report		
2	7	50%
3	4	28.6%
4	2	14.3%
≥5	1	7.1%
Bother from nocturia*		
No problem	1	7.1%
Very small problem	3	21.4%
Small problem	5	35.7%
Medium problem	4	28.6%
Large problem	0	0%
Congestive heart failure history	1	7.1%
Hypertension	8	57.1%

*Missing data from 1 participant

Table 2: Results of ddAVP trial (n=14)

	Mean (s.d.)	T-test vs. baseline	T-test vs. placebo
Nocturia episodes (diary)			
Baseline	2.1 (0.6)		
Max ddAVP	1.4 (0.7)	$P<0.001$	$P=0.10$
Max Placebo	1.7 (0.8)	$P=0.02$	
Nocturnal urine volume			
Baseline	804 mL (273)		
Max ddAVP	608 mL (194)	$P=0.02$	$P=0.01$
Max Placebo	733 mL (224)	$P=0.27$	

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