Is Testing with dDAVP Useful in Detecting Carriers of the Nephrogenic Diabetes insipidus Gene?

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Dear Sir,

Knoers et al. [1] recently examined the fibrinolytic responses to the administration of l-desamino[8-D-argi-nine]vasopressin (dDAVP) in 6 male patients with congenital nephrogenic diabetes insipidus, 6 female carriers and 6 normal control subjects. Tissue-type plasminogen activator activity and antigenicity were not increased in the male patients, whereas normal or delayed responses were observed in the obligatory carriers. Therefore, Knoers et al. concluded that testing with dDAVP was of limited use in carrier detection.

We agree that factor VIIIc, von Willebrand factor and fibrinolytic responses to dDAVP infusion are variable and poor predictors of the carrier state, but we believe that the plasma renin activity response observed after dDAVP administration may be a useful predictor of the carrier state.

We infused dDAVP (0.3 µg/kg of body weight, up to a maximum of 24 µg) during 20 min into 14 male patients with congenital nephrogenic diabetes insipidus, 11 female obligatory carriers and 5 normal subjects (8 studies) [2, 3]. We measured mean arterial pressure, pulse rate, plasma renin activity, plasma cyclic AMP, factor VIIIc, von Willebrand factor, tissue-type plasminogen activator activity and antigenicity before and at various intervals after dDAVP administration. In the normal subjects, mean arterial pressure was decreased by 10–15%, whereas pulse rate was increased by 20–25%, renin activity by 65%, the release of coagulation factors by 2- to 3-fold and fibrinolytic responses by 4- to 12-fold. None of these changes were observed in the patients with congenital nephrogenic diabetes insipidus. Intermediate to normal responses were observed in obligatory carriers except for the plasma renin activity responses illustrated in figure 1

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200 --

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dDAVP infusion

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t $^{3/8}$ - $^{\wedge}$ J:

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-90 -60 -30 0 30 60 90 120 150 180

Time, min

Fig. 1. Plasma renin activity responses to dDAVP infusion (0.3 µg/kg of body weight up to a maximum of 24 µg) in 5 normal subjects (■) (8 studies), 11 obligatory carriers of the hereditary diabetes insipidus gene (A) and 14 male patients with hereditary nephrogenic diabetes insipidus (•). In normal subjects, dDAVP infusion doubled plasma renin activity. Minimal or no changes were observed in the other two groups of patients. * = Significant differences from baseline (values at 0 and 30 min). Error bars are contained within the symbol when not visible [adapted from 3., reprinted from Kidney International with permission].

and 2. We also calculated the area under the curve for the responses of all the different values to dDAVP infusion (figure 3). The plasma renin activity response was again singled out as a potential predictor of the carrier state since it was the only 'negative' response obtained in the obligatory carriers.

The measurement of the plasma renin activity responses (which could be an integral part of the hemodynamic responses) observed after dDAVP infusion is easy to do and is widely available. However, it is recognized

dDAVP and Carriers of the Nephrogenic Diabetes insipidus Gene

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Normal
Obligatory
Nephrogenic
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subjects
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DI

(n = 8)
(n ≈ 11)
(n = 14)

Fig. 2. Plasma renin activity (PRA) individual responses to dDAVP infusion in the three groups of subjects described in figure 1. Results are reported as percents of baseline values observed at 30 min. DI = Diabetes insipidus.

that restriction fragment length polymorphism analysis is far superior for definitive testing. In an earlier publication, Knoers et al. [4] calculated a lod score of 10 for probe DXS52, i.e., the logarithm of the probability of observing coinheritance of two loci, assuming that they are genetically linked, divided by the probability of detecting coinheritance if they are unlinked. Nevertheless, the risk assessments may be hampered in practice by missing information on haplotypes, small families and the lack of informative matings. These genetic tests are less widely available than the plasma renin activity measurements even though they are relatively simple and the samples can easily be shipped to appropriate centers where genetic testing is done. In conclusion, we propose that the measurement of plasma renin activity after dDAVP administration could be potentially useful in predicting the carrier state.

Nephrogenic DI
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I Obligatory carriers
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100 --
50--
-50 J-
MAP
PRA cAMP
vWF FVIIIc Pulse

Fig. 3. Area under the curve obtained for 6 values (von Wille-brand factor, vWF; factor VIIIc, FVIIIc; pulse rate; mean arterial blood pressure, MAP; plasma renin activity, PRA; plasma

cyclic AMP, cAMP) measured after dDAVP infusion in 4 normal subjects, 11 female obligatory carriers for the nephrogenic diabetes insipidus gene and 14 male patients with congenital nephrogenic diabetes insipidus (DI). Areas under the curve from 0 to 120 min were obtained (see fig. 1). Results are expressed as the percent of the mean value observed in normal individuals. In obligatory carriers the plasma renin activity response to dDAVP infusion was negative, the von Willebrand factor, factor VIIIc, pulse and cyclic AMP responses intermediate but the mean arterial blood pressure response was complete.

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