DDAVP (1-desamino-8-D-arginine vasopressin) clearance rate

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Abstract. Utilizing a highly sensitive radioimmunoassay (RIA) for 1-desamino-8-D-arginine vasopressin (DDAVP) and a constant infusion kinetic protocol we measured DDAVP clearance rates (CR) in 6 non-pregnant ewes. Despite mean (and SEM) plasma DDAVP levels as high as 5349 (±151) pg/ml, no changes in blood pressure or heart rate were observed. The CR of DDAVP was 3.6 (±0.2) ml/kg × min. This CR is only 23% of the mean arginine vasopressin (AVP) CR measured in similar animals in an earlier study. The relatively decreased CR of DDAVP appears to account largely for the approximately 5-fold prolongation of antidiuresis of this synthetic derivative relative to AVP.

DDAVP (1-desamino-8-D-arginine-vasopressin) is a highly effective, synthetic derivative of arginine vasopressin (AVP) widely used for the treatment of central diabetes insipidus, (Robinson 1976). Deamination of the terminal amino group at position 9 produced a prolonged antidiuretic effect compared to AVP or lysine vasopressin (LVP), (Coculescu et al. 1977; Dousa et al. 1971; Ford et al. 1975), and substitution of D-arginine for L-arginine at position 8 abolished most of the pressor activity (Sawyer et al 1974a,b; Walker et al. 1969). The precise mechanism of the prolonged antidiuretic activity remains unclear. It has been suggested that DDAVP has increased potency in stimulating renal outer medullary adenylate activity and cyclic AMP production (Seif et al. 1978). In addition, DDAVP seems to be degraded more slowly than AVP (Seif et al. 1978). The half life of DDAVP in the only published study in which DDAVP was measured by radioimmunoassay (RIA) was calculated from plasma disappearance rate following intranasal administration. In that study absorption and clearance were not measured separately and the calculated half life of 0.4 to 4 h represents both processes. In the present study we utilized a constant infusion method in sheep to measure the in vivo metabolic clearance of DDAVP for comparison with earlier data similarly derived for AVP.

Materials and Methods

DDAVP and AVP assay

Plasma and CSF DDAVP levels were measured using a modification of the AVP assay procedure (Skowsky et al. 1974). DDAVP (Bachem Co.) was labelled with 125I using the chloramine T method (Skowsky et al. 1974). Monoiodinated DDAVP was separated by chromatography using a CM-Sephadex column as described earlier for AVP (Skowsky et al. 1974). Antibodies from New Zealand white rabbits immunized according to the method of Skowsky & Fisher (1972), were screened for [125I]DDAVP binding. Antibody R357, which has the highest AVP affinity of any of our AVP antisera, used in a final dilution of 1:800 000 produced about 30% binding of 125I labelled DDAVP. DDAVP standard was obtained from Ferring (0.01% solution in saline and...
chlorbutanol). AVP cross-reactivity with AVP in the RIA system using $^{125}$I labelled DDAVP was 70%, whereas cross-reactivity with oxytocin was less than 2%. Using the RIA system with $^{125}$I labelled AVP, cross-reactivity with DDAVP was 0.4%. Sensitivity of the DDAVP assay was 0.2 pg/tube at 90% binding (B/B0 = 0.9). With this assay method, endogenous immunoreactivity diluted parallel to standard curves in plasma as well as in CSF (with dilutions of 1:2, 1:4 and 1:10). The intra-assay and inter-assay coefficients of variation were 6.2% and 12%, respectively.

Plasma DDAVP was extracted using the bentonite method as described for AVP; CSF DDAVP was assayed in unextracted sample (Reppert et al. 1981). The mean recovery of DDAVP added to DDAVP free sheep plasma was 67 ± 4% (mean ± SEM).

Plasma AVP concentrations were measured by radioimmunoassay as recently described (Skowsky et al. 1974).

Sheep preparation

Carotid artery and jugular vein catheters were placed in 6 healthy ewes (Columbia-Suffolk) under pentobarbital anaesthesia. DDAVP (Bachem Co) was infused iv using constant infusion pumps for a 3 h period in 3 animals and for a 5 h period in 5 additional animals. Baseline blood samples (5 ml) were obtained 20 and 10 min prior to beginning the constant infusions and were repeated at 30, 90, 120 and 180 min after beginning the infusions in the 3 h study animals or hourly after beginning the infusions in the 5 h study animals. Blood samples were collected in iced tubes in 30 µl of 15% potassium EDTA. Each sample was spun in a refrigerated centrifuge and 1 ml plasma samples were stored at -20°C for subsequent measurements of DDAVP, AVP and osmolality. During the DDAVP infusion period, heart rate and blood pressure were monitored continuously and osmolality was measured with a Beckman Digimatic Osmometer Model 3D (Advanced Instruments; Needham Heights, Mass).

DDAVP disappearance rates were calculated as:

$$\text{CR (ml/kg x min)} = \frac{\text{Infusate DDAVP concentration (pg/ml) x infusion rate (ml/min)}}{\text{DDAVP steady state plasma level (pg/ml) x body weight (kg)}}$$

Plasma DDAVP levels were expressed as mean ± SEM in pg/ml; AVP results were measured as µU/ml; 1 µU approximates 2 pg.

Results

The baseline mean plasma AVP level was 1.2 ± 0.6 µU/ml. Three different DDAVP infusion rates were utilized in the study (0.2, 12.5 and 20 ng/min × kg), but only one infusion rate was employed in each study animal. Steady state conditions were achieved after a 2 h infusion period in all animals. The steady state plasma DDAVP levels (Fig. 1) were 73 ± 11 pg/ml (2 animals), 319 pg/ml (1 animal) and 5349 ± 151 pg/ml (3 animals). Mean plasma osmolality decreased during the study period (in all 6 animals) from a baseline of 292 ± 5.4 mOsm/kg to 277 ± 8.9 mOsm/kg by 3 h. This decrease was not significant by 2 way analysis of variance (ANOVA). Heart rate and blood pressure did not change during the DDAVP infusions.

There were no significant differences among CR values measured at high and low DDAVP infusions rates; the mean overall DDAVP CR was 3.6 ± 0.2 ml/kg × min.

Discussion

The mean DDAVP CR (3.6 mg/kg × min) assessed in the present study approximates 20% of the mean AVP CR (17.7 ml/kg × min) measured in the
same breed of adult ewes in an earlier study (Stegner et al. 1984). Coculescu et al. (1977) reported an antidiuresis of 14 h duration following intranasal administration of 10 µg DDAVP; this contrasted with a 4 h antidiuresis observed after intranasal application of 12.5 µg of AVP. Thus, for equivalent 10 µg amounts of DDAVP and AVP the duration of antidiuresis following AVP is about 23% of that of DDAVP. This is in accordance with bioassay studies in the intact rat which demonstrated a 2.5–10-fold prolongation of DDAVP antidiuresis relative to AVP antidiuresis in vivo (Sawyer et al. 1974a,b). These combined results suggest that decreased clearance largely accounts for the prolonged duration of DDAVP antidiuresis. In an earlier report Seif et al. (1978) suggested that other mechanisms contribute to the antidiuresis, including slower absorption from the nasal mucosa and greater potency in stimulating receptor or post-receptor mechanisms of antidiuresis. However, that observation has not been confirmed in other studies (Dousa et al. 1971; Ford et al. 1975). The present results suggest that mechanisms other than decreased clearance are of minor importance in determining the duration of DDAVP antidiuresis.

Despite very high plasma DDAVP levels in the present study, heart rate and blood pressure were unaffected. This observation is consistent with previous data indicating a minimal pressor activity. This provides another advantage over AVP or LVP in the treatment of central diabetes insipidus. However, the major advantage is the prolonged duration of the DDAVP effect. The 4- to 5-fold reduced clearance of DDAVP relative to AVP allows control of diabetes insipidus with twice daily DDAVP dosage. Moreover, the duration of antidiuresis can be prolonged by increasing the dose with a minimum of side effects.

References


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