Pituitary (2017) 20:602–603
DOI 10.1007/s11102-017-0824-8

Combined dexamethasone and desmopressin test in the differential diagnosis of ACTH-dependent Cushing's syndrome and pseudo-cushing's states

A. Verónica Araya[1] · Carmen Romero[1] · Melchor Lemp[1]

Published online: 4 September 2017

Dear Editors,

We believe it is important to report our experience using the combined dexamethasone and desmopressin (Dx/DDAVP) test in the differential diagnosis of ACTH-dependent Cushing's syndrome (CS) and pseudo-Cushing's states (PCS).

Corticotropin-releasing hormone (CRH) is the recommended stimulus for the differential diagnosis of Cushing's disease (CD) and ectopic-ACTH syndrome (EAS). Current guidelines recommend using a combined dexamethasone/CRH test to differentiate CS from PCS. As the pituitary expresses V3 vasopressin receptor, some researchers evaluated the response to lysine vasopressin (LVP) and DDAVP as an alternative stimulus. Nevertheless, according to other authors DDAVP does not show good specificity in the differential diagnosis between CD and EAS for ACTH response [1]. On the other hand, some reports have shown that the use of a 10 μg intravenous (IV) dose, alone or combined with Dx, results in sensitivity and specificity that is similar or higher than CRH in the differential diagnosis of CD with PCS [2].

In some countries, CRH is not available everywhere. Moreover, CRH and ACTH measurements are expensive. For this reason, LVP and later DDAVP have been in use in our center since the 1980s in a stimulation cortisol test, for the differential diagnosis of ACTH-dependent CS. In order to distinguish the non-Cushing's subjects, we recommended an overnight dose of 1 mg of oral Dx.

We performed a retrospective analysis of forty-four patients, collected between 1996 and May of 2017. Thirty-six CD (29 females/7 males; mean age: 36.7 ± 14.6 years), confirmed by increased ACTH (70.5 ± 47 pg/ml), cortisol suppression (more than 50%) in the Tyrrel test, pituitary adenoma in radiological examinations and at the surgical specimen, an adenoma with positive ACTH stain in most of the tumoral cells. Eight patients (seven females/one male; age: 44.7 ± 15.7 years) with EAS (ACTH: 53.3–1000 pg/ml) corresponded to: thymus and pancreas carcinoids, two lung carcinomas, pheochromocytoma, liver metastasis from neuroendocrine tumor and two occults. These cases had negative sellar MR and biochemical results that were not compatible with pituitary origin. Dx/DDAVP test was also performed in nine females (age: 35.4 ± 11.3 years) corresponded to PCS and seven control subjects (two females/five males; age: 33.8 ± 15 years). All patients and controls signed an informed consent according to our local Research Ethics Committee.

The morning after Dx dose, two basal blood samples were taken. Afterward, 8 μg of DDAVP was given by an IV injection and sampling for cortisol measurements was initiated: (15–120 min). Women were not taking oral contraceptives.

Previously, we described four types of cortisol responses in Dx/LVP test: positive suppression and negative response to LVP, observed in normal subjects; negative suppression and positive response, in subjects with CD; both, negative suppression and response in subjects with non-pituitary CS; and an equivocal response with both positive suppression and positive response [3].

We used cortisol suppression cutoff of 1.8 μg/ml. For a positive response to DDAVP, we consider the same value at the Dx/LVP test: maximal cortisol response over 6 μg/ml observed between 15 and 45 min post-stimulus [3]. Figure 1 illustrates the pattern of responses.

✉ A. Verónica Araya
varaya@rhcuch.cl

[1] Universidad de Chile Clinical Hospital, Santos Dumont 999-Independencia, Santiago, Chile

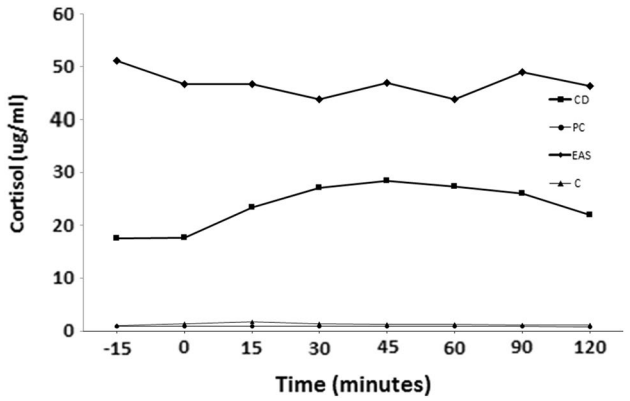

Fig. 1 Patterns of response to 8 µg of IV DDAVP at time 0 in subjects with Cushing's disease (CD), ectopic-ACTH syndrome (EAS), pseudo-Cushing's states (PC) and controls (C). One mg of dexamethasone was administered orally the day before at 11 pm

In order to discriminate between CD and EAS, Dx/DDAVP test had a sensitivity of 89% and specificity of 100%. No patient with EAS responded to DDAVP, but four patients with CD did not attain the 6 µg/ml increase. In these patients, petrosal sinus sampling was performed.

So as to discriminate between CD and PCS and controls, the test had a sensitivity of 96.9% and specificity of 93.7%. One patient with CD suppressed cortisol under cutoff post Dx, but responded to DDAVP instead; a control patient did not suppress cortisol, but also did not respond to DDAVP.

By using a DDAVP dose lower than described by other research groups and also evaluating the cortisol response, we were able to obtain similar results to those previously demonstrated with the CRH test.

This combined Dx/DDAVP test reached over 90% sensitivity and specificity for differential diagnosis of PCS, compared with a previous report (81.5 and 90%, respectively) [2]. The equivocal responses may be observed in any test, and so far, 100% of specificity and sensitivity have not been demonstrated, which is the clinical criteria in the analysis of results that will help us in making the correct diagnosis.

The lack of dexamethasone levels determination during the test is a limitation of this study, as well as, the limited size of pseudo-Cushing's and EAS groups. Nevertheless, these factors are similar to other reports and with strong enough results. Thus, we consider that combined test with overnight Dx/DDAVP and cortisol measurement is a useful tool in the study of ACTH-dependent Cushing's syndrome and pseudo-Cushing's states when CRH is not available, and resources are limited.

Compliance with ethical standards

Conflict of interest Authors A. Veronica Araya, Carmen Romero and Melchor Lemp declares that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional Research Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Terzolo M, Reimondo G, Alì A, Borretta G, Cesario F, Pia A, Pacotti P, Angeli A (2001) The limited value of desmopressin test in the diagnostic approach to Cushing´s syndrome. Clin Endocrinol 54, 609–616
2. Tirabassi G, Papa R, Faloia E, Boscaro M, Arnaldi G (2011) Corticotrophin-releasing hormone and desmopressin tests in the differential diagnosis between Cushing's disease and pseudo-Cushing state: a comparative study. Clin Endocrinol 75:666–672
3. Contreras P, Araya V (1996) Overnight dexamethasone pretreatment improves the performance of the lysine-vasopressin test in the diagnosis of Cushing's syndrome. Clin Endocrinol 44:703–710