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A Combined Test Using Desmopressin and Corticotropin-Releasing Hormone in the Differential Diagnosis of Cushing's Syndrome

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ABSTRACT

To assess the ability of desmopressin to differentiate between pituitary and ectopic ACTH-dependent Cushing's syndrome and to determine whether diagnostic accuracy could be improved by administering it together with human sequence CRH, we examined its effects on cortisol and ACTH secretion when given alone or in combination with CRH in patients with Cushing's syndrome of varied etiology and compared these data to the results of a standard CRH test in the same individuals.

Each patient was studied on three occasions, in random order, separated by at least 48 h. At 0900 h, via an indwelling forearm cannula, 10 μg desmopressin, 100 μg CRH, or a combination of the two were given as an iv bolus; thereafter, blood was drawn every 15 min for 2 h. The responses to the individual agents were determined according to the timing and calculation criteria suggested by Nieman *et al.* (1993). A total of 25 patients with Cushing's syndrome were studied: 17 patients with pituitary-dependent Cushing's syndrome, Cushing's disease (CD); 5 patients with occult ectopic ACTH secretion (EC); and 3 patients with primary adrenal (ACTH-independent) Cushing's syndrome.

In this series, the best discrimination among ACTH-dependent patient groups was achieved using the combined test. Using the responses of plasma cortisol, all 17 patients with CD showed a rise greater than any of the 5 patients with EC, whereas 1 patient with CD showed a plasma ACTH response within the range seen in the patients with EC. Plasma cortisol responses to desmopressin alone were seen in 14 of 17 patients with CD and 1 of 5 patients with EC and, after CRH alone, in 15 of 17 patients with CD but in no patient with EC. In contrast, plasma ACTH responses after CRH alone were seen in 14 of 17 patients with CD and 2 of 5 patients with EC and, after desmopressin alone, in 12 of 17 with CD and 3 of 5 with EC, thus indicating overlapping responses between the groups and poorer discrimination. No responses were seen in the ACTH-independent group.

These data indicate that desmopressin causes the secretion of ACTH and cortisol in patients with ACTH-dependent Cushing's syndrome, and that in combination with CRH, it may provide an improvement over the standard CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. Furthermore, these data suggest that there may be abnormalities in vasopressin receptor function or number in ACTH-secreting tumors. (*J Clin Endocrinol Metab* **82:** 176–181, 1997)

CRH IS A POTENT stimulus for the secretion of ACTH in man (1, 2) and is used in the CRH test, which has been extensively validated in the investigation and differentiation of the causes of Cushing's syndrome (3–5). CRH causes a significant rise in plasma ACTH and cortisol in the majority of patients with pituitary-dependent Cushing's syndrome, Cushing's disease (CD), whereas such effects are seen only rarely in patients with the ectopic ACTH syndrome (EC) (6–8). For many years it has been known that vasopressin also stimulates ACTH release and, in particular, that it potentiates the ACTH-releasing effects of CRH (9). These actions are thought to occur via the specific corticotroph vasopressin receptor, the V_3 or V_{1b} receptor, which has recently been cloned (10, 11). Lysine vasopressin and arginine vasopressin have been shown to have ACTH-releasing properties similar to those of CRH when administered to patients with Cushing's syndrome (12), although CRH appears to better discriminate between ectopic ACTH and pituitary disease (13). Furthermore, side-effects consisting of abdominal pain, nausea, and flushing have precluded the routine clinical use of vasopressin for diagnostic testing, although it has been suggested that it may be better tolerated when used as a low dose infusion in combination with CRH (14).

Desmopressin, a long acting analog of vasopressin (15), has relative specificity for the renal V_2 receptor, with little V_1-mediated pressor activity (16). Although its specific V_{1b} receptor activity is uncertain, it has been shown previously to have no intrinsic *in vivo* ACTH-releasing characteristics when given as an infusion in man (17). Desmopressin has, however, been shown to cause a significant release of cortisol and ACTH in the majority of patients with CD when given as bolus, but not in one patient with EC, and it has, therefore, been suggested that it may be used to aid the differential diagnosis of the causes of ACTH-dependent Cushing's syndrome (18). However, previous studies have not explored whether the combination test of desmopressin and CRH would be better than either peptide alone in the differential diagnosis.

The present study, therefore, was designed to assess the effects of desmopressin on the release of ACTH and cortisol when given as an iv bolus dose, alone or in combination with

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CRH, to patients with Cushing's syndrome and thus to compare the clinical utility of desmopressin and CRH as diagnostic tests. Human sequence CRH was used instead of the ovine sequence (19), as it is currently more widely available internationally.

Subjects and Methods

A total of 25 consecutive patients were studied on 3 occasions separated by at least 48 h: 17 patients with pituitary-dependent Cushing's syndrome (CD; mean age, 42 yr; range, 11–73 yr), 5 patients with EC (3 women, 33, 34, and 39 yr old, with bronchial carcinoid tumors; a male, 34 yr old, with a medullary cell carcinoma of the thyroid; and a male, 62 yr old, with a disseminated carcinoid syndrome; all were occult insofar as no tumor was apparent clinically or on simple radiographic investigation), 1 female patient with a functioning adrenocortical carcinoma (65 yr old), 1 woman with a functioning adrenocortical adenoma (61 yr old), and 1 male patient (51 yr old) with ACTH-independent massive macronodular hyperplasia. The cause of Cushing's syndrome was verified histologically after surgery in 24 of the 25 patients. In the remaining patient, all clinical features and biochemical evaluations, including the high dose dexamethasone test (8 mg/day for 48 h) and CRH-stimulated inferior-petrosal catheter studies, were completely consistent with CD, but he did not undergo transsphenoidal hypophysectomy. No patient was receiving any drug known to affect the hypothalamo-pituitary-adrenal axis. All patients gave written informed consent to the investigation, which was approved by the ethical committee of St. Bartholomew's Hospital.

After an overnight fast, an in-dwelling forearm cannula was inserted at 0830 h; the subject remained supine for the remainder of that day's study. At 0900 h (0 min), 10 μg desmopressin (DDAVP, Ferring, Malmo, Sweden) and saline placebo for CRH, 100 μg human sequence CRH (Ferring, Malmo, Sweden) and saline placebo for desmopressin, or a combination of these peptides were injected sequentially over periods of 15 s each. Blood was taken for estimation of plasma ACTH and cortisol at −15, 0, 15, 30, 45, 60, 90, and 120 min. Blood pressure and pulse rate were recorded by automated means (Dinamapp, Tampa, FL) at each sampling point. After testing, each subject was advised to restrict fluid intake to 2 L for the remainder of the day. The order of all investigations was randomized and run in a single blind manner.

Calculation of response criteria

Following the suggested criteria of Nieman *et al.* (20) using the ovine CRH test, we calculated in each patient group the percent rise in the mean circulating plasma ACTH values at 15 and 30 min and circulating plasma cortisol values at 30 and 45 min above the mean basal values at −15 and 0 min, after the administration of human CRH, desmopressin, or a combination of the two. The response criteria documented by Nieman *et al.* (20) that best discriminated Cushing's disease from the ectopic ACTH syndrome were a 20% rise in circulating plasma cortisol and a 35% rise in circulating plasma ACTH; these criteria were assessed in this study.

Assays

Plasma cortisol was measured by an in-house unextracted nonchromatographic RIA; the coefficient of variation at 100 and 1000 nmol/L was 6% (21). Plasma ACTH was measured by our routine in-house Vycor (Societe-A.T.A. Geneva, Switzerland) glass-extracted RIA originally developed in 1971, which has subsequently been validated using a range of chromatographic procedures in human studies (22).

Results

Plasma cortisol responses (Table 1 and Fig. 1)

Differential effects of CRH or desmopressin given alone. Using the response criterion of at least a 20% rise in the circulating plasma cortisol level, calculated from the ratio of the mean values at 30 and 45 min over the mean basal value (21), 15 of 17 patients with CD responded positively to CRH, but no responses were seen in the patients with EC. Using the same response criterion, 14 of 17 patients with CD responded to desmopressin, as did patient 21 with an ACTH-secreting medullary carcinoma of the thyroid. Patients 1, 2, 5, and 17 with CD showed discordant responses to CRH and desmopressin; patients 1 and 17 responded only to desmopressin, whereas patients 2 and 5 responded only to CRH (Table 1). No responses to either treatment were seen in the patients with ACTH-independent Cushing's syndrome.

Differential responses to CRH and desmopressin in combination. Calculating the response of plasma cortisol to the injection of CRH plus desmopressin from the same time points, every patient with CD showed a response higher than that of any of the patients with EC. The lowest response in any patient with CD was 38%, whereas the highest response in the EC group was 29%. Thus, discrimination (based upon the degree of increase) between groups was seen using this test alone.

Plasma ACTH responses (Table 2 and Fig. 2)

Differential effects of CRH and desmopressin given alone. Using the response criterion of at least a 35% rise in plasma ACTH calculated from the ratio of the mean of the values at 15 and 30 min over the mean basal level (21), 14 of 17 patients with CD and 2 of 5 patients with EC (patients 18 and 22) responded to CRH alone. After the administration of desmopressin alone, 12 of 17 patients with CD and 3 patients with EC showed such a response (patients 19, 20, and 21). After CRH alone, 6 patients, and after desmopressin alone, 9 patients with CD responded within the range of responses seen in the patients with EC. Patients 1, 2, 5, and 17 had the same discordant responses to CRH and desmopressin using ACTH response criteria as they demonstrated using cortisol criteria (see above). Patient 4 showed a cortisol, but apparently not an ACTH, response to CRH. ACTH remained undetectable in all 3 patients with primary adrenal disease.

Differential effects of the combination of CRH and desmopressin. Using the same time points to calculate a response after desmopressin and CRH were given together, the EC group's responses were between 138–306%, whereas the responses in the CD group ranged from 350-4319%, except in patient 17, who demonstrated a 71% rise.

Side-effects

After the administration of either peptide, adverse effects were limited to a short-lived flushing sensation (1–15 min), which was similar in nature to that after the combination treatment, but slightly longer in duration (2–20 min). After the combination treatment, three patients experienced a slight metallic taste in their throats, lasting 2–5 min. In no case was there evidence of water overload. There was no significant change in blood pressure in any patient; two patients experienced a transient (<5 min) sinus tachycardia after the combination treatment (maximum heart rates, 113 and 100 beats/min), with no symptomatic palpitations, chest pain, or fall in blood pressure.

TABLE 1. Plasma cortisol responses in 17 patients with Cushing's disease (CD), 5 patients with the ectopic ACTH syndrome, and three patients with primary adrenal Cushing's syndrome

Patient	Age (yr)	CRH (100 μg, iv) treatment: Plasma cortisol (nmol/L)			Desmopressin (10 μg, iv): Plasma cortisol (nmol/L)			CRH (100 μg, iv) and desmopressin (10 μg, iv): Plasma cortisol (nmol/L)		
		Basal B	Mean at 30–45 min	% Rise: B to mean of 30–45 min	Basal B	Mean at 30–45 min	% Rise: B to mean of 30–45 min	Basal B	Mean at 30–45 min	% Rise: B to mean of 30–45 min
CD										
1	73F	1163	1191	2	1169	1792	53	1367	1891	38
2	61M	994	1297	31	807	696	−14	584	929	59
3	38F	453	729	61	411	679	65	485	817	69
4	28F	531	661	24	438	878	100	504	1006	100
5	48F	558	757	36	716	718	0.2	605	959	59
6	25F	371	688	85	479	785	64	452	880	95
7	40F	434	571	32	379	520	37	338	571	69
8	33F	450	679	51	464	906	95	334	813	143
9	52F	229	855	274	398	984	147	281	830	196
10	39F	418	820	96	456	772	64	569	1110	95
11	32M	675	994	47	885	1094	24	391	983	152
12	53F	517	1009	95	535	1431	168	541	1145	112
13	11M	297	843	183	307	700	128	332	962	190
14	14F	624	787	26	335	949	184	328	770	135
15	46F	602	1032	72	517	580	12	511	993	94
16	62F	530	904	71	788	1357	72	531	1103	108
17	61F	673	796	18	764	943	23	569	828	45
Mean ± SEM		560 ± 58	859 ± 48	71 ± 17	579 ± 60	928 ± 89	72 ± 15	513 ± 61	976 ± 69	103 ± 12
Ectopic ACTH										
18	33F	569	672	18	778	784	0.7	598	769	29
19	39F	1319	1400	6	817	903	11	652	839	29
20	49F	1598	1689	6	1271	1507	19	1256	1520	21
21	34M	654	726	11	1373	1696	23	1256	1476	17
22	62M	1690	1811	7	ND	ND	ND	1484	1892	28
Mean ± SEM		1166 ± 263	1259 ± 267	10 ± 3	1060 ± 177	1222 ± 258	13 ± 6	1049 ± 199	1299 ± 240	25 ± 3
Primary adrenal Cushing's										
23	65F	525	546	4	485	486	0.3	604	784	30
24	51M	489	486	−0.7	467	421	−10	ND	ND	ND
25	61F	778	688	−12	439	579	7	564	553	−2.0
Mean ± SEM		597 ± 112	573 ± 73	−3 ± −6	497 ± 27	495 ± 56	0.7 ± 6	584 ± 30	668 ± 163	14 ± 23

ND, Not determined.

Discussion

Our data suggest that desmopressin causes ACTH and cortisol secretion when given on its own to patients with ACTH-dependent Cushing's syndrome. As a test, however, when given alone it did not reliably distinguish between Cushing's disease and the ectopic ACTH syndrome. In this and another series, CRH has a high discriminatory power when given alone, but absolute discrimination between groups is not achieved with the human sequence peptide; indeed, utilization of the ACTH responses resulted in an unacceptably low degree of specificity. When desmopressin is given in combination with CRH, we found that enhanced discrimination may be made between the ACTH-dependent groups, as a greater response is seen in patients with CD than in those with EC. After the combination treatment, a rise of over 38%, calculated from the average of the 30 and 45 min plasma cortisol samples, over the basal levels at −15 and 0 min was seen in all patients with CD, whereas in all five patients with EC it was less than this, with the highest rise in plasma cortisol being 29%. Interestingly, the plasma ACTH responses provided less discrimination, as one patient with pituitary disease demonstrated a rise within the range seen in the patients with EC. Furthermore, the test was well tolerated, with minimal symptomatic and no adverse effects, in a wide age range of patients. Asymptomatic sinus tachycardia of short duration was observed, but did not cause any cardiovascular compromise in any patient.

Vasopressin has a well documented synergistic effect with CRH for ACTH release (9, 23, 24). Desmopressin has similar ACTH-releasing effects in rats *in vitro* (25), and this effect is not reversed by V_2 receptor antagonists (26). Previous data in normal volunteers have not demonstrated either direct or potentiating effects of desmopressin for ACTH release when coadministered with CRH (17). Desmopressin is said to be a specific V_2 receptor agonist, and this may explain the lack of response of ACTH secretion in the normal volunteers. Desmopressin does, however, as shown in this study and previously (18), cause significant release of ACTH and cortisol in ACTH-dependent Cushing's syndrome. Glucocorticoids have recently been shown to up-regulate the expression of the V_{1b} receptor in normal rat anterior pituitary glands and rescue the down-regulation seen after adrenalectomy, with similar effects reported in the vasopressin-deficient Brattleboro rat (27); thus, such up-regulation may be caused by hypercortisolemia rather than changes in vasopressin levels (27). Furthermore, the majority of human corticotroph adenomas and some ACTH-secreting bronchial carcinoids have been demonstrated to express high levels of the V_{1b} receptor;

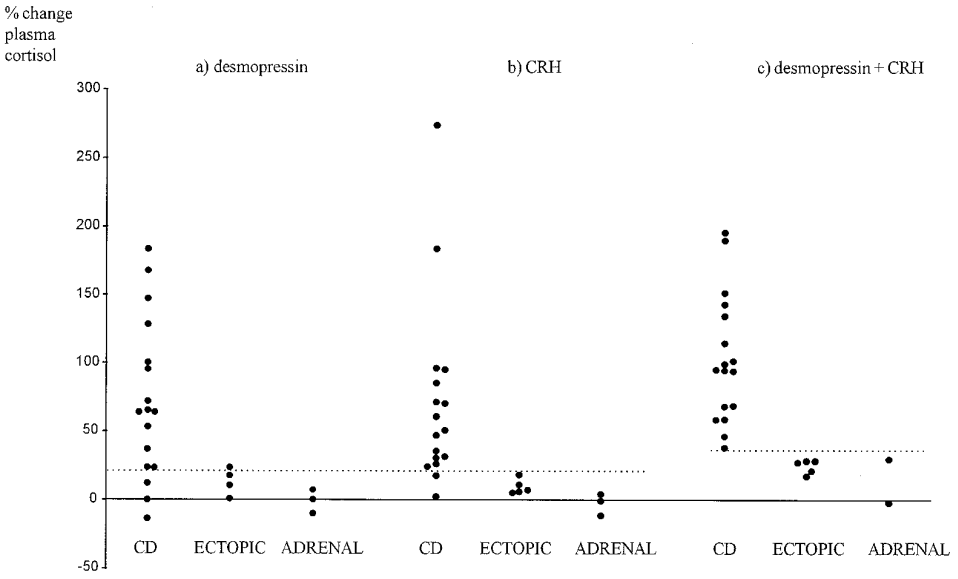

FIG. 1. Percent change in plasma cortisol (mean of 30 and 45 min values *vs.* mean basal values at −15 and 0 min) in 17 patients with CD, 5 patients with EC, and 3 patients with an primary adrenal Cushing's syndrome after the administration of 1) desmopressin (10 μg, iv), 2) human sequence CRH (100 μg, iv), or 3) CRH (100 μg, iv) plus desmopressin (10 μg, iv; *dashed line* represents 20% for the CRH alone and desmopressin alone tests and 38% for the CRH plus desmopressin test).

TABLE 2. Plasma ACTH responses in 17 patients with Cushing's disease (CD) and 5 patients with the ectopic ACTH syndrome

Patient	Age (yr)	CRH (100 μg, iv): Plasma ACTH (pg/mL)			Desmopressin (10 μg, iv): Plasma ACTH (pg/mL)			CRH (100 μg, iv) and desmopressin (10 μg, iv): Plasma ACTH (pg/mL)		
		Basal B	Mean at 15–30 min	% Rise: B to mean of 15–30 min	Basal B	Mean at 15–30 min	% Rise: B to mean of 15–30 min	Basal B	Mean at 15–30 min	% Rise: B to mean of 15–30 min
CD										
1	73F	45	55	21	40	769	1846	54	2660	4319
2	61M	77	286	271	36	32	−11	37	167	350
3	38F	29	227	681	27	97	257	43	429	897
4	28F	25	28	14	10	33	225	10	100	900
5	48F	18	28	53	19	20	3	17	79	376
6	25F	12	24	109	10	22	120	16	115	642
7	F	43	111	160	36	88	146	40	238	495
8	33F	13	41	215	17	66	285	13	138	958
9	52F	10	66	555	15	34	134	12	123	921
10	39F	21	190	824	24	97	311	12	135	1074
11	32M	143	226	59	302	363	20	66	870	1228
12	53F	17	69	318	16	182	1038	20	231	1085
13	11M	16	91	469	18	37	103	13	109	772
14	14F	16	13	−22	12	102	787	15	105	621
15	46F	61	314	414	43	46	6	39	303	687
16	62F	15	111	666	22	141	541	19	270	1318
17	61F	47	65	37	49	53	8	50	85	71
Mean ± SEM		36 ± 8	114 ± 24	285 ± 68	41 ± 17	128 ± 46	342 ± 121	28 ± 4	345 ± 139	983 ± 230
Ectopic ACTH										
18	33F	23	37	61	72	95	32	36	146	305
19	39F	96	126	31	64	90	41	73	173	138
20	49F	119	142	19	80	143	78	56	125	125
21	34M	29	33	14	27	80	194	29	113	295
22	62M	81	154	90	ND	ND	ND	72	206	188
Mean ± SEM		69 ± 11	98 ± 15	43 ± 8	61 ± 6	102 ± 7	86 ± 19	53 ± 5	152 ± 9	210 ± 21

ND, Not determined.

in contrast, the CRH receptor is expressed in corticotroph adenomas, but far less commonly in bronchial carcinoid tumors (28, 29). Taken together, these studies suggest that the effect of desmopressin in these tumors may be mediated by up-regulation of the V_{1b} receptor in neuroendocrine tissue, which, in turn, may reflect prevailing hypercortisolemia. It seems probable that desmopressin may show cross-affinity with the V_{1b} receptor when it is present in high concentrations, although it is also possible that up-regulation or aberrant expression of the V_2 receptor in ACTH-secreting cells may occur. Further, it is possible that the differentiating ability of the combined test may relate to a greater increase in the co-overexpression of the CRH and V_{1b} receptors in many of the corticotroph adenomas than in ectopic tumors secreting ACTH and the higher response seen in CD.

A previous report has suggested that desmopressin is a

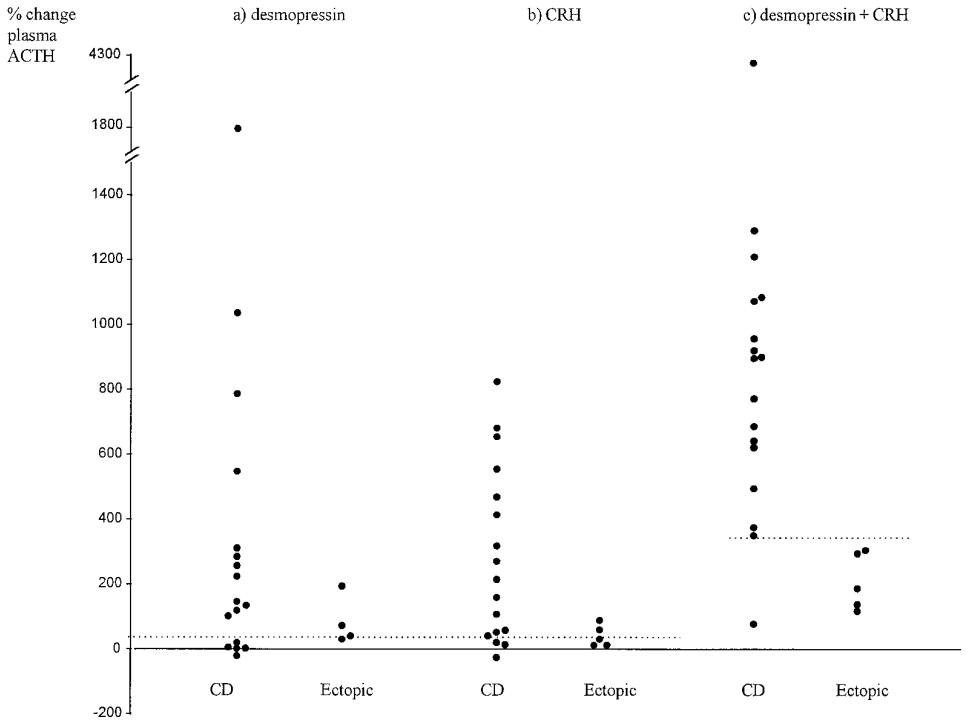

FIG. 2. Percent change in plasma ACTH (mean of 15 and 30 min values *vs.* mean basal values at −15 and 0 min) in 17 patients with CD and 5 patients with EC after the administration of 1) desmopressin (10 μg, iv), 2) human sequence CRH (100 μg, iv), or 3) CRH (100 μg, iv) plus desmopressin (10 μg, iv; *dashed line* represents 35% for the CRH alone and desmopressin alone tests and 350% for the CRH plus desmopressin test).

readily available and cost-effective alternative to CRH in the investigation of Cushing's syndrome (18). Certainly, in this study it seems to have a similar, but inferior, ability to differentiate between CD and EC when analyzing either plasma ACTH or cortisol responses. Clearly, three of our five patients with EC responded to desmopressin given alone.

In conclusion, desmopressin given alone appears to cause the release of ACTH and cortisol in ACTH-dependent Cushing's syndrome. Such effects of desmopressin suggest abnormalities in receptor number or function in these neuroendocrine ACTH-secreting tumors that merit further study. As a diagnostic test, human sequence CRH alone appears to be better than desmopressin alone in discriminating between ACTH-dependent groups, whereas the combination of the two appears to produce better results than either alone. Occult ectopic ACTH-secreting tumors can be extremely small and may offer a considerable diagnostic challenge, behaving in many ways similarly to eutopic corticotroph tumors (30). Thus, the combined test may be of considerable diagnostic utility. This is, however, a relatively small series of patients, and the percent rise criterion that distinguishes pituitary from ectopic ACTH production may need alteration with the benefit of further experience. Although we do not suggest that this combination test replace the standard CRH test, it seems probable that testing with these agents in addition to conventional testing with the high dose dexamethasone suppression test or inferior petrosal catheter studies may be of considerable clinical benefit.

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References

1. **Grossman A, Kruseman AC, Perry L, et al.** 1982 New hypothalamic hormone, corticotropin-releasing factor, specifically stimulates the release of adrenocorticotrophic hormone and cortisol in man. Lancet. 1:921–922.
2. **Orth DN, DeBold CR, Decherney GS, et al.** 1982 Pituitary microadenomas causing Cushing's disease respond to corticotropin-releasing factor. J Clin Endocrinol Metab. 55:1017–1019.
3. **Chrousos GP, Schulte HM, Oldfield EH, Gold PW, Cutler Jr GB, Loriaux DL.** 1984 The corticotropin-releasing factor test. An aid in the evaluation of patients with Cushing's syndrome. N Engl J Med. 310:622–626.
4. **Trainer PJ, Grossman A.** 1991 The diagnosis and differential diagnosis of Cushing's syndrome [Review]. Clin Endocrinol (Oxf). 34:317–330.
5. **Orth DN.** 1992 Corticotropin-releasing hormone in humans. Endocr Rev. 13:164–191.
6. **Hermus AR, Pieters GF, Pesman GJ, Smals AG, Benraad TJ, Kloppenborg PW.** 1986 The corticotropin-releasing-hormone test *versus* the high-dose dexamethasone test in the differential diagnosis of Cushing's syndrome. Lancet. 2:540–544.
7. **Nieman LK, Chrousos GP, Oldfield EH, Averingos PC, Cutler Jr GB, Loriaux DL.** 1986 The ovine corticotropin-releasing hormone stimulation test and the dexamethasone suppression test in the differential diagnosis of Cushing's syndrome. Ann Intern Med. 105:862–867.
8. **Grossman AB, Howlett TA, Perry L, et al.** 1988 CRF in the differential diagnosis of Cushing's syndrome: a comparison with the dexamethasone suppression test. Clin Endocrinol (Oxf). 29:540–544.
9. **DeBold CR, Sheldon WR, DeCherney GS, et al.** 1984 AVP potentiates ACTH release induced by ovine CRF. J Clin Invest. 73:533–538.
10. **de Keyzer Y, Auzan C, Lenne F, et al.** 1994 Cloning and characterisation of the human V_3 pituitary vasopressin receptor. FEBS Lett. 356:215–220.
11. **Sugimoto Y, Sato M, Mochizuki S, et al.** 1994 Molecular cloning and functional expression of a cDNA encoding the human V_{1b} vasopressin receptor. J Biol Chem. 269:27088–27092.
12. **Catania A, Cantalamessa L, Orsatti A, et al.** 1984 Plasma ACTH-response to the corticotropin-releasing factor in patients with Cushing's disease. Comparison with the lysine-vasopressin test. Metabolism. 33:478–481.
13. **Taberin A, San Gailli F, Dezou S, et al.** 1990 The corticotropin-releasing factor test in the differential diagnosis of Cushing's syndrome: a comparison with the lysine vasopressin test. Acta Endocrinol (Copenh). 123:331–338.
14. **Bertagna X, Coste J, Raux-Demay MC, Letrait M, Strauch G.** 1994 The combined corticotropin-releasing hormone/lysine vasopressin test discloses a corticotroph phenotype. J Clin Endocrinol Metab. 79:390–394.
15. **Edwards CRW, Kitau MJ, Chard T, Besser GM.** 1973 Vasopressin analog

DDAVP in diabetes insipidus: clinical and laboratory studies. Br Med J. 579:375–378.
16. **Sawyer WH, Acosta M, Balaspiri L, Judd J, Manning M.** 1974 Structural changes in the arginine vasopressin molecule. Endocrinology. 94:1106–1115.
17. **Gaillard RC, Riondel AM, Ling N, Muller AF.** 1988 Corticotropin-releasing factor activity of CRF 41 in normal man is potentiated by angiotensin II and vasopressin but not by desmopressin. Life Sci. 43:1935–1944.
18. **Malerbi DA, Mendonca BB, Liberman B, et al.** 1993 The desmopressin test in the differential diagnosis of Cushing's syndrome. Clin Endocrinol (Oxf). 38:463–472.
19. **Trainer PJ, Faria M, Newell-Price JDC, et al.** 1995 A comparison of the effects of human and ovine corticotropin-releasing hormone on the pituitary adrenal axis. J Clin Endocrinol Metab. 80:412–417.
20. **Nieman LK, Oldfield EH, Wesley R, Chrousos GP, Loriaux DL, Cutler GB.** 1993 A simplified morning ovine corticotropin-releasing hormone stimulation test in the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab. 77:1308–1312.
21. **Cunnah D, Jessop DS, Besser GM, Rees H.** 1986 Measurement of circulating corticotropin-releasing factor in man. J Endocrinol. 113:123–131.
22. **McLoughlin L, Evans SF, Watson JD, Hinds CJ, Rees LH.** 1988 Characterisation of circulating pro-opiomelanocortin-related peptides in human septic shock. J Endocrinol. 199:159–165.
23. **Gillies G, Linton EA, Lowry PJ.** 1979 Corticotropin-releasing activity of the new CRF is potentiated several times by vasopressin. Nature. 299:355–357.
24. **Rivier C, Rivier J, Mormède P.** 1983 Studies of the nature of the interaction between vasopressin and corticotropin-releasing factor on adrenocorticotropin release in the rat. Endocrinology. 115:882–886.
25. **Knepal W, Homolka L, Vlaskovska M, Nutto D.** 1984 *In vitro* adrenocorticotropin/β-endorphin-releasing activity of vasopressin analogs is related neither to pressor nor to antidiuretic activity. Endocrinology. 114:1797–1804.
26. **Buckingham JC.** 1986 Vasopressin receptors influencing the secretion of ACTH by the rat adenohypophysis. J Endocrinol. 113:389–396.
27. **Lolait SJ, Aguilera G.** Regulation of pituitary vasopressin receptor (V_{1b}) mRNA by adrenolectomy and glucocorticoids [Abstract P1–570]. Proc of the 77th Annual Meet of The Endocrine Soc. 1995.
28. **de Keyser Y, Lenne F, Auzan C, et al.** 1995 The pituitary vasopressin receptor V3 receptor and the corticotroph phenotype in ectopic ACTH syndrome. J Clin Invest. 97:1311–1318.
29. **Dahia PLM, Ahmed-Shuaib A, Jacobs RA, et al.** 1996 Vasopressin receptor expression and mutation analysis in corticotropin-secreting tumours. J Clin Endocrinolol Metab. 81:1768–1771.
30. **de Keyser Y, Clauser E, Bertagna X.** 1996 The pituitary V3 vasopressin receptor and the ectopic corticotropin syndrome. Curr Opin Endocrinol Diabetes. 3: 125–131.

Erratum

In the Editorial "Tibolone as an Alternative to Estrogen for the Prevention of Postmenopausal Osteoporosis in Selected Postmenopausal Women," by B. Lawrence Riggs, MD, *(Journal of Clinical Endocrinology and Metabolism,* **81:** 2417–2418, 1996), the footnote at the bottom of page 2417 gave the wrong information for corresponding with the author.

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The printer regrets this error.