

ESE Recommendation on CRH Shortage: scope of the problem and how to address it

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Scope of the problem

Ferring Pharmaceuticals has been the main supplier of corticotropin-releasing hormone (CRH) in the world. Ferring provided the statement that CRH is not being manufactured anymore due to the breakdown of essential production equipment. The unavailability of stock duration is currently unknown and there is no clear indication on future timelines. This imposes a threat on the availability of CRH worldwide. While other suppliers of CRH may emerge, alternative diagnostic approaches are required, particularly for the work-up of adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome (CS), where CRH is most useful. Here, the European Society of Endocrinology (ESE) will provide a recommendation regarding this issue.

CRH in the differential diagnosis of ACTH-dependent CS

CRH has been extensively used as a testing agent for differential diagnosis of ACTH-dependent CS (1-3). CRH stimulation test aims to distinguish between pituitary and extra-pituitary ACTH source, and its usefulness is clearly stated in current guidelines on CS (4-6). In contrast to non-pituitary ACTH-dependent CS, CRH administration leads to a rise in plasma ACTH and serum cortisol in most patients with pituitary ACTH-dependent CS (3,7-10). Consequently, ACTH and cortisol responses to CRH can be useful in the diagnosis of ACTH-dependent CS, although it should be used with other biochemical and imaging procedures (4,5).

Alternative tests for the differential diagnosis of ACTH-dependent CS in the absence of CRH:

High Dose Dexamethasone Suppression Test (HDDST): As ACTH-secreting pituitary tumours are more susceptible to dexamethasone suppression than ectopic tumours, substantial cortisol suppression during HDDST could support the diagnosis of Cushing's disease (CD). There are currently two versions of this test, but for convenience and to minimize issues with compliance we recommend using the overnight HDDST (**see test protocols**). Serum cortisol suppression by 50% and 80% has a specificity of 60-90% and 87-100% for CD, respectively (11-15). However, as ACTH-secreting pituitary tumours may also be markedly resistant to dexamethasone suppression, minor or no suppression of cortisol during HDDST does not rule out CD (11-14).

Desmopressin Test: This test is performed in the morning and involves serial blood cortisol and ACTH measurements following intravenous injection of desmopressin (**see test protocols**). Desmopressin is a synthetic analog of the endogenous neuropeptide arginine-vasopressin. As ACTH-secreting pituitary tumours can express aberrant V3 vasopressin receptors, desmopressin infusion may stimulate ACTH secretion from these cells (16). Thus, ACTH and cortisol increase following desmopressin injection support the diagnosis of CD: 20% rise in serum cortisol and 50% rise in plasma ACTH provide a specificity of 40-75% and 40-100%, and a sensitivity of 73-90% and 76-100% for CD, respectively (30, 32, 33). In a recent meta-analysis, a positive response

was associated with a similar sensitivity to the CRH test, but sub-optimal specificity with a number of positive responses in ectopic CS (17). Indeed, some ectopic tumours, especially well differentiated neuroendocrine tumours (NETs), may also express vasopressin receptors, leading to false positive results. Hence, desmopressin test results should be interpreted along with other diagnostic tests. Combining the desmopressin test and HDDST may increase the overall test specificity (17). 20% rise in serum cortisol and 30% rise in plasma ACTH on the desmopressin test, along with 50% suppression of serum cortisol on HDDST provide a specificity of 91% (13,18).

Cross-sectional imaging alternatives: Magnetic resonance imaging (MRI) is the modality of choice for the localization of ACTH-producing pituitary adenomas (19). If the tumour size is >10 mm, it is accepted as the source of ACTH production, and pituitary surgery is indicated. In smaller tumours, additional diagnostic steps are needed to distinguish between pituitary and ectopic ACTH production. The sensitivities and specificities for detecting small pituitary adenomas are highly dependent on MRI protocols. If the ACTH source is not identified using standard MRI protocols, supplementary sequences can be used and may localize up to 80-90% of corticotroph tumours (20). Whole body thin-slice scans may be used for localizing tumours secreting ACTH ectopically. The first study to consider is a contrast-enhanced neck and chest computed tomography (CT) scan, followed by CT and/or MRI of the abdomen and pelvis (21,22).

Functional hybrid imaging alternatives: ¹¹C-methionine positron emission tomography (Met-PET) has been successfully used to detect small ACTH-producing pituitary tumours (23), but its availability is limited. If ectopic ACTH syndrome is considered, and cross-sectional imaging studies are negative, somatostatin analog scintigraphy may help (⁶⁸Ga-DOTA-somatostatin analog PET/CT or ¹¹¹In-pentetreotide SPECT/CT). ⁶⁸Ga-DOTA-somatostatin analog PET provides the highest sensitivity (88-93%) (24). ¹⁸F-FDG PET/CT also has a role in the diagnostic algorithm, but is reserved for grade 3 NETs or neuroendocrine carcinomas (sensitivity >90%) (25).

Inferior Petrosal Sinus Sampling (IPSS) with desmopressin: By determining central-to-peripheral ACTH gradient, IPSS is considered the gold standard test in discriminating CD from ectopic CS in patients with ACTH-dependent CS (4-6). Still, false negative tests for CD diagnosis are witnessed in some cases, possibly due to anatomical and biochemical variations of the disease. The unavailability of CRH will impact IPSS results, as basal unstimulated values do not perform optimally in comparison to those after stimulation (26,27). Since ACTH stimulation during IPSS improves its performance, CRH has been used in most centers. Sensitivity and specificity of IPSS using CRH are 98% and 100%, respectively (28). However, only a few studies have been conducted on IPSS using desmopressin (**see test protocols**), so its use and clinical experience is still limited. Yet, most available data shows that IPSS with desmopressin is safe and increases test performance (sensitivity of 94-97%, and specificity of 98-100%), so its use may be considered (28-30).

Combined diagnostic alternatives: Combining the various biochemical and imaging tests may increase the sensitivity and specificity of investigations in ACTH-dependent CS (17,18,21).

In case of CRH shortage, we recommend to use a combination of alternative tests including desmopressin test, HDDST, pituitary MRI, whole-body thin-slices CT, and finally IPSS with desmopressin if the tests are not concordant in indicating a pituitary ACTH source, if the clinical context suggests an ectopic origin (e.g. severe hypertension, oedema, sarcopenia, sudden onset of clinical picture, hypokalaemia, severe hypercortisolism) despite negative whole body imaging and if an MRI is not conclusive in indicating a pituitary adenoma.

CRH in the diagnosis of Central Adrenal Insufficiency

Secondary or tertiary adrenal insufficiency (caused by inadequate secretion of either ACTH from the pituitary or CRH from the hypothalamus leading to glucocorticoid deficiency) summarized as central adrenal failure, are predominantly due to pituitary diseases or pharmacotherapy (e.g. exogenous glucocorticoids), and represent the vast majority of cases with adrenal insufficiency (31,32). One rationale for using the CRH stimulation test here is a subtype-specific ACTH response (i.e., stable levels in secondary and increasing levels in tertiary adrenal insufficiency). The main indication is establishing central adrenal insufficiency per se. However, the remarkably lower sensitivity and specificity of CRH stimulation test compared to other dynamic testing procedures like the insulin tolerance test (ITT) must be considered (33). Historically, the ITT has been considered as the gold standard test (**see test protocols**). The shift towards the ACTH stimulation test (**see test protocols**) as a first-line diagnostic tool for the evaluation of suspected central adrenal insufficiency in patients with pituitary disorders is reflected by current national guidelines (34-36). Impaired hypothalamic-pituitary function with concomitant lack of CRH and/or ACTH will over time lead to adrenal atrophy. After a few weeks, even administration of supraphysiological ACTH doses will not result in adequate cortisol stimulation, thereby confirming central adrenal insufficiency. According to two meta-analyses different test protocols offer similar diagnostic accuracy (37,38).

Alternative dynamic function tests for evaluating the hypothalamic-pituitary-adrenal (HPA) axis include the metyrapone test and the glucagon stimulation test (**see test protocols**) (33). The metyrapone test seems to be very sensitive in the detection of central adrenal insufficiency (particularly of partial HPA impairment which may be overlooked during ACTH stimulation test). However, as low levels of both serum cortisol and 11-deoxycortisol are required for making the diagnosis, the test is currently not widely applied (availability of 11-deoxycortisol measurements is still limited). Glucagon is a weaker stimulant of the HPA axis in comparison to other tests (ITT or high-dose ACTH stimulation test) and may be associated with a broad range of (usually moderate) adverse effects.

Other utilizations of CRH

Ruling out non-neoplastic hypercortisolism (NNH)/pseudo-Cushing states (pCS) with first-line testing may be inconclusive due to false-positive results (39). Several second-line tests have been proposed including CRH stimulation test, but there is still no agreement on the gold standard approach. The combined dexamethasone-CRH test assumes that only pituitary ACTH-dependent CS patients will sustain a cortisol response to CRH stimulation after dexamethasone suppression, allowing to differentiate CS from NNH/pCS. Based on the different pattern of vasopressin receptor expression in pituitary corticotroph adenoma cells compared to normal corticotroph cells, desmopressin test demonstrated high detection accuracy for NNH/pCS (40). **In the case of CRH shortage, we recommend the use of desmopressin test.**

Undetectable plasma ACTH levels are the hallmark of ACTH-independent CS while mildly reduced levels (10-20 pg/mL) do not reliably indicate adrenal cortisol secretion. In the latter cases dynamic testing with CRH has been suggested to evaluate pituitary responsiveness, thereby differentiating ACTH-dependent from ACTH-independent CS (with strong vs absent ACTH responses to CRH). CRH test may also be useful in the diagnostic work-up of primary

bilateral macronodular adrenal hyperplasia with hypercortisolism, where positive ACTH response to CRH is associated with higher remission rates following unilateral adrenalectomy (41,42). **If CRH is unavailable, there is no alternative dynamic test to the CRH stimulation test that could be recommended in patients with ACTH-independent CS.**

Other sources of CRH

In Europe, the main provider of CRH has been Ferring, however CRH vials are also produced and distributed by other companies. For example, in Japan, CRH is produced by Tanabe and distributed by Nipro Es Pharma; in Europe, CRH is distributed and can be purchased through [Unipharma](#) based in Switzerland. Whether CRH will be available from these alternative sources in appropriate amounts, for reasonable costs and over long periods of time is currently unknown.

Exemplary short test protocols

High Dose Dexamethasone Suppression Test (HDDST): One version consists of taking 2 mg of oral dexamethasone every 6 hours for 2 days (8 doses) and urinary free cortisol collected in the second day or serum morning cortisol measured after the last dose. The other version is the **overnight HDDST** and it relies on taking 8 mg of oral dexamethasone at 23:00 and measuring serum cortisol the next morning (43).

Desmopressin Test: In the morning and following an overnight fast, blood samples for ACTH and cortisol measurements are collected prior to and then 15, 30, 45, 60, 90 and 120 min after intravenous bolus injection of undiluted 10 µg desmopressin (43).

Inferior Petrosal Sinus Sampling (IPSS) with desmopressin: At baseline, blood samples for ACTH measurements are collected simultaneously from bilateral IPSS and peripheral vein, and collected again 3, 5, and 10 min after peripheral intravenous bolus injection of undiluted 10 µg desmopressin (30).

ACTH stimulation test: Serum samples for cortisol measurement are taken at 0, 30 and 60 min after i.v. or i.m. administration of 250 µg synthetic ACTH as bolus (43).

Insulin tolerance test (ITT): After i.v. administration of fast acting insulin (0.1 U/kg bodyweight in suspected hypopituitarism, 0.2 U/kg bodyweight in acromegaly or diabetes) as bolus injection, both a serum glucose nadir < 40 mg/dl (2.2 mmol/L) and symptoms of hypoglycemia are required as evidence of adequate stress. Samples for blood glucose and cortisol are taken at 0, 15, 30, 45, 60, 90, and 120 min. This test should be carried out by experienced staff (43).

Metyrapone test: Metyrapone is orally administered at midnight with a fatty snack (e.g. milk). Drug doses are calculated according to bodyweight (2.0 g if < 70 kg, 2.5 g if 70-90 kg, 3.0 g if > 90 kg). Blood samples for measurement of ACTH, cortisol, and 11-deoxycortisol are collected between 8:00 and 9:00 the next morning (43).

Glucagon stimulation test: Glucagon is administered intramuscularly (e.g. in the deltoid muscle). Drug doses are calculated according to bodyweight (1.0 mg if ≤ 90 kg, 1.5 mg if > 90 kg, smaller doses in children). Blood samples for cortisol are collected after 0, 90, 120, 150, and 180 min (44).

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