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Use of the low-dose corticotropin stimulation test for the diagnosis of secondary adrenocortical insufficiency

使用低劑量促腎上腺皮質激素刺激試驗診斷繼發性腎上腺皮質缺乏症

Objective. To assess the clinical utility and safety of the low-dose corticotropin stimulation test in the diagnosis of secondary adrenocortical insufficiency.
Design. Prospective study.
Setting. Regional hospital, Hong Kong
Participants. Seventy-two Chinese patients with suspected secondary adrenocortical insufficiency.
Main outcome measure. Serum cortisol response during the low-dose corticotropin stimulation test, using the insulin tolerance test as the gold standard.
Results. The 30-minute cortisol level during the low-dose corticotropin stimulation test was most closely correlated (r=0.79) with the peak cortisol level achieved during the insulin tolerance test. The optimum sensitivity and specificity of the low-dose corticotropin stimulation test were obtained at a cut-off value of 550 nmol/L or more for the 30-minute cortisol level. Using the insulin tolerance test as the gold standard for comparison, the low-dose corticotropin stimulation test had a sensitivity of 97%, a specificity of 78%, a positive predictive value of 81%, and a negative predictive value of 97% at this cut-off value. The positive likelihood ratio was 4.4 and the negative likelihood ratio 0.04.
Conclusion. The low-dose corticotropin stimulation test, using the cortisol response at 30 minutes after synacthen 1 μg is a safe, convenient, and sensitive method for screening abnormalities of the hypothalamic-pituitary-adrenocortical axis in Chinese patients suspected of having secondary adrenocortical insufficiency.

目的：評估低劑量促腎上腺皮質激素刺激試驗，在診斷繼發性腎上腺皮質缺乏症中的效用及安全性。
設計：預期研究。
安排：香港一所地區醫院。
參與者：72 名懷疑患有繼發性腎上腺皮質缺乏症的華裔患者。
主要結果測量：利用胰島素耐量試驗作為標準，量度低劑量促腎上腺皮質激素刺激試驗時血清皮質醇的反應。
結果：在低劑量促腎上腺皮質激素刺激試驗期間，於30分鐘時的皮質醇水平與在胰島素耐量試驗中，皮質醇所達到的頂水平相關性最高(r=0.79)。當臨界值達 550 nmol/L 或以上時， 30 分鐘時的皮質醇水平在低劑量促腎上腺皮質激素刺激試驗中有最佳的靈敏度和專一性。使用胰島素耐量試驗作標準，並用相同臨界值進行比較時，低劑量促腎上腺皮質激素刺激試驗的靈敏度為 97%，專一性為 78%，正預測值為 81%，而負預測值則為 97%。正可能性比為 4.4，負可能性比為 0.04。
結論：為懷疑患有繼發性腎上腺皮質缺乏症的華裔患者檢查丘腦下垂體腎上腺皮質軸，低劑量促腎上腺皮質激素刺激試驗(當使用 1 μg 的 synacthen 後及利用在 30 分鐘時的皮質醇反應)是一種安全、方便和靈敏的方法。

Key words:
Adrenal gland hypofunction;
Corticotropin;
Diagnosis

關鍵詞：
腎上腺機能減退；
促腎上腺皮質激素；
診斷

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Introduction

Early recognition of adrenocortical insufficiency is important because if left untreated, it may cause refractory hypotension and even death during acute

physiological stress. Symptoms and signs of adrenocortical insufficiency are, however, non-specific and diagnosis can be difficult. Various biochemical tests have been used to exclude and/or confirm the diagnosis in patients with conditions that may compromise the integrity of the hypothalamic-pituitary-adrenocortical axis, such as pituitary diseases or the chronic use of medicinal steroids. Each of these tests has advantages and disadvantages. The insulin tolerance test (ITT) has traditionally been considered the gold standard for assessing secondary adrenocortical insufficiency.[1,2] This test, however, carries the risk of hypoglycaemia, and is contraindicated for patients with epilepsy, ischaemic heart disease, or who have recently had a cerebrovascular accident. The metyrapone test has been employed,[3] but measurement of 11-deoxycorticosterone is not readily available in most laboratories, and metyrapone may also precipitate shock in some patients.[4] Other tests such as the corticotropin-releasing hormone stimulation test[5] or the glucagon stimulation test[6] are not as sensitive and specific as ITT.

Moreover, all of the above-mentioned tests are labour intensive and inconvenient. They require multiple blood sampling and are poorly accepted by patients, especially those who have to undergo the test on a regular basis. Simpler tests, such as fasting or spot cortisol levels, show significant overlap between healthy subjects and patients with secondary adrenocortical insufficiency.[7] The conventional dose corticotropin stimulation test, using synthetic adrenocorticotropic hormone (ACTH) 250 μg, has been criticised for suboptimal sensitivity in relatively mild cases of secondary adrenocortical insufficiency.[8,9] This test has been reported to give false negative results in up to 30% of cases.[10,11] This is attributed to the use of a supraphysiological dose of ACTH, leading to pharmacological stimulation of partially atrophic adrenals in secondary adrenocortical insufficiency. In 1964, Landon et al[12] demonstrated that ACTH 3 μg could elicit a maximal adrenocortical response. Dickstein et al[13] showed that, in healthy individuals, ACTH 1 μg elicited a cortisol response equivalent to that elicited by ACTH 250 μg. A number of recent studies have suggested that the corticotropin stimulation test using ACTH 1 μg is more sensitive than that using 250 μg, without significant loss of specificity.[14-17] Some authors have advocated replacing ITT with a low-dose corticotropin stimulation test (LDCST), while others have queried the sensitivity and specificity of LDCST.[18,19] Uncertainty also remains with respect to the optimal timing of blood sampling and the most cost-effective way of completing LDCST, as well as the optimal cut-off values to be used.[20] The aims of this study were:

(1) to assess the usefulness of LDCST in the diagnosis of patients with suspected secondary adrenocortical insufficiency, using ITT as the gold standard diagnostic test; and
(2) to identify the optimal timing of blood sampling, the most efficient way of completing the test, and the optimal cut-off values for LDCST in our patient population.

Methods

This study was carried out at the Endocrine Clinic of Queen Elizabeth Hospital between March 1997 and December 2000. The patients invited to participate in the study had clinically suspected secondary adrenocortical insufficiency. Patients with contraindications for ITT such as epilepsy or ischaemic heart disease were excluded. Patients who had severe hypocortisolism, as evidenced by a fasting cortisol of less than 50 nmol/L, were also excluded. All participants underwent a LDCST, followed by an ITT 4 to 7 days apart. Patients receiving chronic steroid therapy for other medical illnesses were advised to cease steroid therapy 1 week before the tests. Written consent was obtained from all patients before both tests.

The LDCST was performed by a specialty nurse. On the day of the test, synthetic ACTH 250 μg (1 ampoule) was added to normal saline 500 mL. After mixing thoroughly, 2 mL (containing 1 μg ACTH) of the freshly mixed solution was withdrawn into a syringe. The patient fasted overnight. Fasting cortisol was taken at 9am the next day, followed by an intravenous bolus injection of ACTH 1 μg. Blood was sampled for cortisol measurement at 20, 30, and 45 minutes after injection for the initial 21 patients, and thereafter at 30 minutes only for the subsequent 51 patients.

The ITT was performed by a specialty nurse supervised by a doctor. The patients fasted overnight. Actrapid insulin (NovoNordisk, Bagsvaerd, Denmark) 0.1 U/kg was given intravenously after a baseline blood sample was taken for glucose and cortisol assay. Diabetic patients receiving insulin treatment were given actrapid insulin 0.15 U/kg plus 50% of their morning dose of short-acting insulin. Bedside haemoglucostix (Surestep Plus; Lifescan, Milpitas, US) testing was performed at 15-minute intervals and blood was sampled for laboratory glucose assay. When hypoglycaemia developed (bedside haemoglucostix result of less than 2.2 mmol/L and occurrence of hypoglycaemic symptoms), a blood sample was taken for glucose and cortisol assay, and 50% dextrose solution 40 mL was given to the patient intravenously, followed by oral food. If hypoglycaemia had not occurred by 45 minutes, an additional dose of actrapid insulin 0.1 U/kg was given. Blood sampling for cortisol measurement was done at intervals of 15 minutes during the first 60 minutes, and thereafter at 30-minute intervals. Cortisol was assayed by the chemiluminescence method (Bayer-Centaur, New York, US). The coefficient of variation for the assay was less than 5%.

Results

Seventy-two Chinese patients completed the study—30 males and 42 females. Ages ranged from 28 to 74 years (mean, 46 years). Clinical reasons for suspicion of dysfunction of the hypothalamic-pituitary-adrenocortical axis were: nasopharyngeal carcinoma with radiotherapy to the

pituitary region (n=22), iatrogenic Cushing's syndrome (n=20), non-functioning pituitary macroadenoma (n=14), empty sella syndrome (n=8), acromegaly (n=5), Sheehan's syndrome (n=1), Cooley's anaemia with secondary haemochromatosis (n=1), and prolactin-secreting pituitary macroadenoma (n=1). All patients were followed up for a mean period of 19.2 months (range, 10-46 months) after the LDCST. Patients with normal ITT results were not given steroids. None of them developed clinical features of adrenocortical insufficiency during follow-up.

Among the 21 patients who had cortisol measurement performed at 20, 30, and 45 minutes after ACTH 1 μg, peak cortisol level was achieved at 20 minutes for six patients, at 30 minutes for 11 patients, and at 45 minutes for four patients (Table 1). The 30-minute cortisol level showed the best correlation (r=0.79) with peak cortisol level achieved during ITT (Fig 1). Correlation coefficients between peak cortisol values during ITT and the 0-minute, 20-minute, 45-minute, and peak cortisol values during LDCST were 0.45, 0.76, 0.69, and 0.76, respectively. No extra information was gained by checking cortisol levels at 20 and 45 minutes in addition to 30 minutes.

For the ITT, it is widely accepted that adrenocortical insufficiency can be excluded if the peak cortisol level is 550 nmol/L or higher. The sensitivity and specificity of LDCST at different 30-minute cortisol cut-off values are shown in Table 2. Receiver operating characteristic (ROC) curve analysis for LDCST (Fig 2) showed that the optimal 30-minute cortisol cut-off value was 550 nmol/L. Of the 72 patients studied, 28 patients had values of 550 nmol/L or higher in both tests (true negatives), 35 had cortisol values lower than 550 nmol/L in both tests (true positives). Eight patients had cortisol values of 550 nmol/L or higher during ITT but lower than 550 nmol/L during LDCST (false positives) and one had a cortisol value of 550 nmol/L or higher during LDCST but lower than 550 nmol/L during ITT (false negatives), giving a sensitivity of 97% (95% confidence interval [CI], 94%-100%), a specificity of 78% (95% CI, 68%-88%), a positive predictive value of 81%, and a negative predictive value of 97% for LDCST when compared with ITT. The positive likelihood ratio was 4.4 and the negative likelihood ratio 0.04.

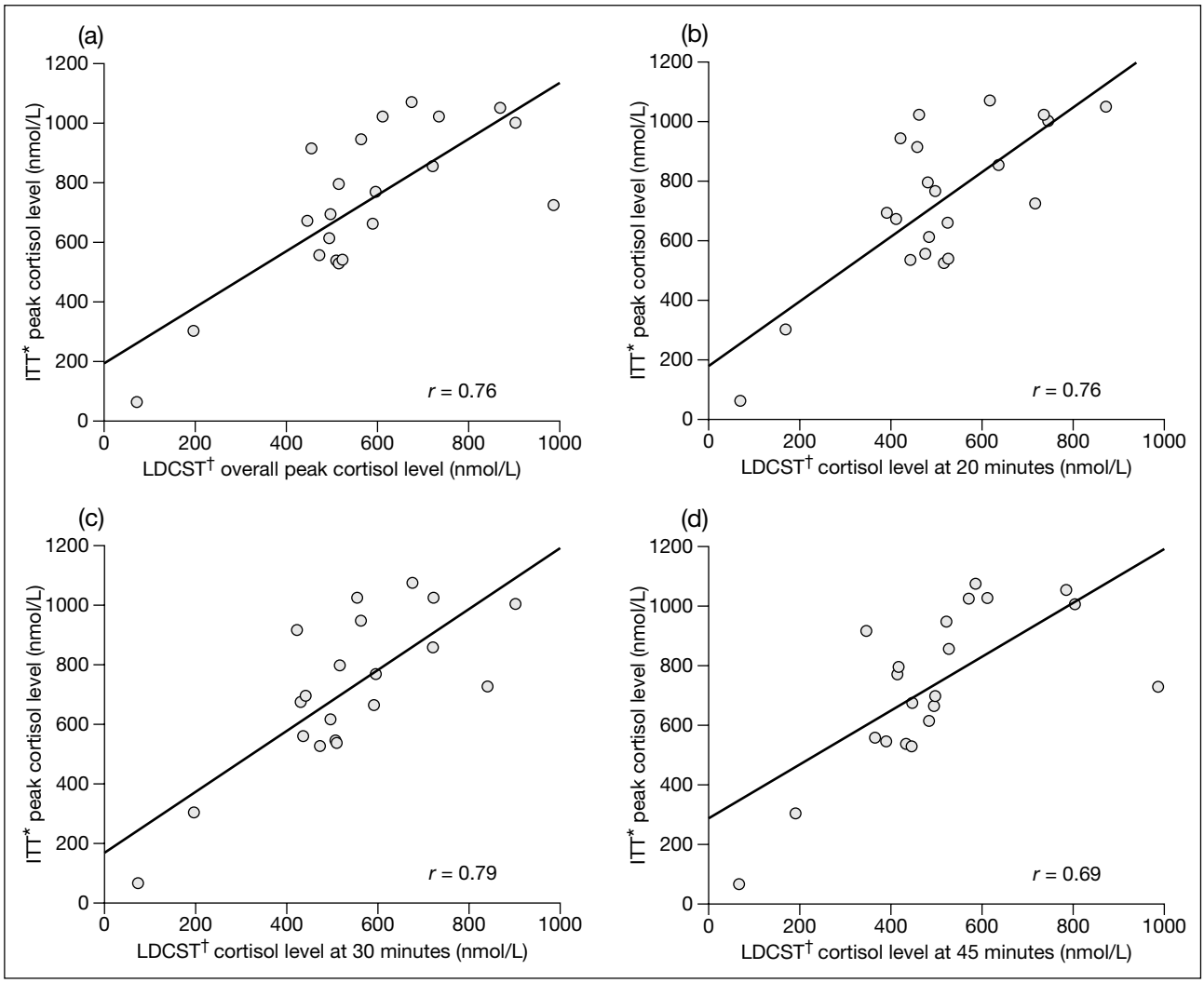
The 30-minute cortisol value after LDCST in the only patient with a false negative result at LDCST was 593 nmol/L, and the peak cortisol value after ITT was 514 nmol/L. Clinically, this patient had nasopharyngeal carcinoma and no symptoms of adrenocortical insufficiency. He was advised to take hydrocortisone during times of stress because of the positive ITT, and LDCST was repeated 6 months later, giving a 30-minute cortisol value of 320 nmol/L. Regular hydrocortisone replacement was given after the second LDCST.

The characteristics of eight patients who had false positive results on LDCST are shown in Table 3. Their 30-minute cortisol levels ranged between 417 and 536 nmol/L after LDCST. No difference in age, sex, body mass index, diagnosis, duration of disease, medication, renal and liver function tests, and concomitant pituitary hormone deficiencies were found between this group of patients and those who had concordant results for both LDCST and ITT.

Fasting morning cortisol values for the 72 patients varied from 51 to 537 nmol/L. The ROC curve for fasting morning cortisol (Fig 2) demonstrated significantly lower sensitivity and specificity at all cut-off values when compared with LDCST. All patients who had a fasting morning cortisol level of 420 nmol/L or more had adequate cortisol response during both ITT and LDCST. All patients with a

Table 1. Cortisol levels at different time intervals after injection of adrenocorticotropic hormone 1 μg compared to peak cortisol levels after the insulin tolerance test

Patient No.	Sex	Clinical diagnosis	Cortisol levels (nmol/L) during low-dose corticotropin stimulation test				Peak cortisol level (nmol/L) during insulin tolerance test
			0 mins	20 mins	30 mins	45 mins	
1	M	Acromegaly	227	495	595	415	766
2	F	Empty sella syndrome	420	743	901	803	1002
3	F	Nasopharyngeal carcinoma	143	389	441	496	692
4	M	Nasopharyngeal carcinoma	54	166	196	190	302
5	F	Empty sella syndrome	292	714	839	986	724
6	M	Empty sella syndrome	345	516	471	447	524
7	F	Nasopharyngeal carcinoma	290	482	495	483	612
8	M	Pituitary non-functioning macroadenoma	161	455	424	345	912
9	M	Nasopharyngeal carcinoma	159	616	676	585	1070
10	F	Sheehan's syndrome	52	66	74	66	62
11	F	Empty sella syndrome	217	525	509	390	544
12	M	Nasopharyngeal carcinoma	280	634	720	526	855
13	F	Empty sella syndrome	206	418	563	521	946
14	F	Empty sella syndrome	340	410	430	447	673
15	F	Pituitary non-functioning macroadenoma	180	460	553	612	1021
16	F	Acromegaly	289	479	514	417	794
17	F	Nasopharyngeal carcinoma	341	521	590	495	660
18	F	Empty sella syndrome	367	870	864	784	1049
19	M	Pituitary non-functioning macroadenoma	499	734	722	569	1023
20	M	Iatrogenic Cushing's syndrome	273	474	436	363	557
21	M	Pituitary non-functioning macroadenoma	298	441	510	432	537



* ITT insulin tolerance test
LDCST† low-dose corticotropin stimulation test

Fig 1. Correlation between peak cortisol level during the insulin tolerance test and (a) overall peak cortisol level during the low-dose corticotropin stimulation test, (b) cortisol level at 20 minutes during the low-dose corticotropin stimulation test, (c) cortisol level at 30 minutes during the low-dose corticotropin stimulation test, and (d) cortisol level at 45 minutes during the low-dose corticotropin stimulation test (n=21)

fasting morning cortisol level of 112 nmol/L or lower had an inadequate cortisol response to ITT.

None of the participants experienced side-effects from the administration of synthetic ACTH. The test was well received by all patients because of its safety and convenience.

Discussion

As it measures cortisol response during hypoglycaemia, a potentially life-threatening situation, the ITT has traditionally been considered the gold standard for assessing secondary adrenocortical insufficiency. However, because

Table 2. Sensitivity and specificity of low-dose corticotropin stimulation test at different 30-minute cortisol cut-off values, using peak cortisol value of 550 nmol/L during insulin tolerance test as the gold standard

Cut-off cortisol level (nmol/L)	True positive	True negative	False negative	False positive	Sensitivity (%)	Specificity (%)
300	7	36	29	0	19	100
400	10	36	26	0	28	100
450	17	35	19	1	47	97
500	23	32	13	4	64	89
530	34	29	2	7	94	81
550	35	28	1	8	97	78
580	35	25	1	11	97	69
600	36	20	0	16	100	56
630	36	17	0	19	100	47
650	36	16	0	20	100	44
700	36	11	0	25	100	31

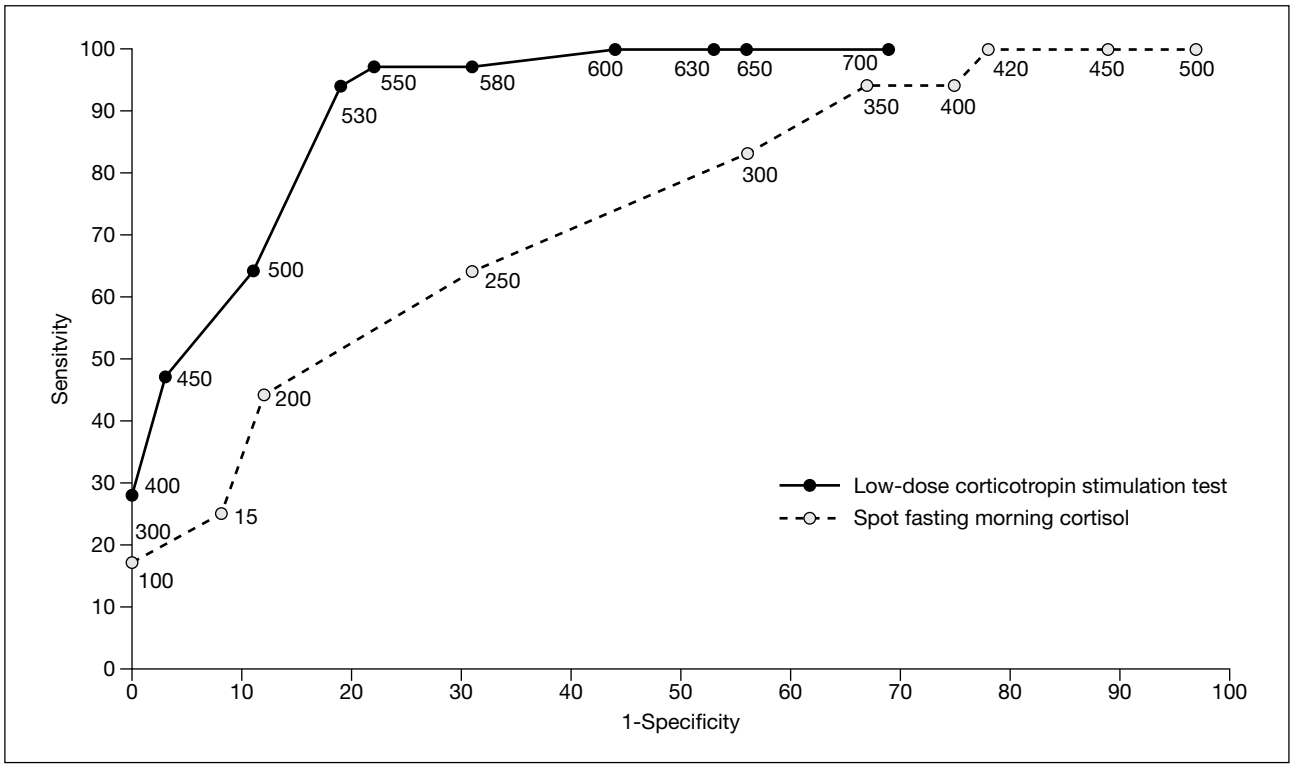


Fig 2. Receiver operating characteristic curves of 30-minute cortisol value during low-dose corticotropin stimulation test and spot fasting morning cortisol

The optimal cut-off value for the 30-minute cortisol level during low-dose corticotropin stimulation test is shown to be 550 nmol/L. Numbers represent the different cut-off values employed for calculation of sensitivity and specificity

it is inconvenient and labour intensive to administer, and carries with it the risk of hypoglycaemia, various attempts have been made to replace ITT with a simpler test. The corticotropin stimulation test using ACTH 250 μg gained favour because of its safety and ease of administration, but has been criticised for lack of sensitivity in patients with milder forms of secondary adrenocortical insufficiency.[8-11] Since untreated adrenocortical insufficiency may result in refractory hypotension and death if patients develop an acute illness or are subjected to the stress of trauma or surgery, it is important to employ a test with high sensitivity to avoid missing positive cases. In 1995, Tordjman et al[21] suggested that higher sensitivity might be achieved by using a lower and more physiological dose of ACTH. Various studies of LDCST have been performed to validate this hypothesis. Discrepant results were reported, either because of differences in the nature of the sample population, small sample size, or use of different cut-off values (Table 4). The cut-off value was assumed to be the same as for ITT in some studies,[14-18,22] whereas others derived the value from a population of healthy individuals,[19,23,24] taking as abnormal values that fell below two standard deviations of the normal mean value or below the 5th percentile of the control population.

To identify the optimal timing of blood sampling and the most cost-effective way of completing LDCST, we measured cortisol levels at 20, 30, and 45 minutes after ACTH 1 μg in the first 21 subjects who participated in this study. The 30-minute cortisol level was most closely correlated with the peak cortisol level after ITT. Analysis showed that no additional information was gained by checking cortisol levels at 20 and 45 minutes in addition to 30 minutes. It thus appears most cost-effective to check only the 30-minute cortisol level after ACTH when doing LDCST.

Although checking a spot morning cortisol level is simpler than doing a stimulation test, the ROC curve (Fig 2) for fasting morning cortisol showed that its sensitivity and specificity at all cut-off values were so low as to preclude its use for the diagnosis of secondary adrenocortical insufficiency. If a fasting morning cortisol value is available for a particular patient and is greater than 420 nmol/L or less than 110 nmol/L, our data suggest that further testing is not necessary, as all patients with these levels in the study were shown to have a healthy or an inadequate response to ITT, respectively. There is no other role for a spot morning cortisol in the diagnosis of adrenocortical insufficiency.

It is obviously desirable to have a test that is both highly sensitive and specific. Unfortunately, there is often a trade-off between the sensitivity and specificity of a diagnostic test. For tests that produce a range of values, the location of a cut-off point on the continuum between normal and abnormal is an arbitrary decision, and the choice of this cut-off point often depends on the designated clinical use of the test. When it is used to rule out a diagnosis, especially a diagnosis that carries with it an important penalty when missed, and when it is used during the early stages of diagnostic evaluation, it is important to choose a cut-off value

Table 3. Characteristics of eight patients who had false positive results at low-dose corticotropin stimulation test

Patient No.	Age (years)/sex	Body mass index (kg/m²)	Medical diseases	Disease duration (years)	Medication
1	34/F	23.3	NPC* (post-RT†)‡	4	Nil
2	60/M	24.1	Pituitary macroadenoma (Post-OT§),‡ HT‖	0.5	Nifedipine retard, premarin, provera
3	58/F	28.2	Empty sella syndrome‡	8	Nil
4	66/F	25.2	Acromegaly (post-OT/RT),‡ HT	2	Bromocriptine, atenolol
5	42/F	21.4	NPC (post-RT)‡	3	Nil
6	70/M	26.8	Iatrogenic Cushing's syndrome,‡ osteoarthritis of the knee, diabetes mellitus, HT, ischaemic heart disease	4	Non-steroidal anti-inflammatory drugs, pepcidine, nifedipine retard, perindopril, gliclazide, isosorbide, aspirin
7	68/F	23.6	NPC (post-RT),‡ temporal lobe epilepsy	20	Sustanon, thyroxine, carbamazepine
8	49/F	26.3	Iatrogenic Cushing's syndrome,‡ asthma	5	Salbutamol, ipratropium, theophylline

* NPC nasopharyngeal carcinoma
† RT radiotherapy
‡ These are diseases leading to the clinical suspicion of secondary adrenocortical insufficiency
§ OT operation
‖ HT hypertension
¶ N normal

Table 4. Performance of low-dose corticotropin stimulation test compared with gold standard in reported studies

Studies	Patients	Gold standard	Cut-off value (nmol/L cortisol)	Patients with impaired HPA*	True positive/ false negative
Abdu et al[15]	42	ITT†	500	12	12/0
Ambrosi et al[22]	57	ITT	500	14	10/4
Mayenknecht et al[18]	44	ITT/MPT‡/ CRH§	535	23	15/8
Nye et al[19]	16	ITT	378	5	4/1
Rasmuson et al[16]	27	ITT	550	16	15/1
Soule et al[23]	65	MPT	414	12	6/6
Talwar et al[14]	24	ITT	550	13	13/0
Tordjman et al[17]	62	ITT	500	19	18/1
Suliman et al[11]	51	MPT	550	15	14/1
Current study	72	ITT	550	36	35/1
Total	460			165	141/15

* HPA hypothalamic-pituitary-adrenocortical axis
† ITT insulin tolerance test
‡ MPT metyrapone test
§ CRH corticotropin-releasing hormone stimulation test

that yields a high sensitivity level. For example, the low cut-off value of 378 nmol/L used by Nye et al[19] (derived from the mean cortisol level minus two standard deviations in nine healthy individuals) might have contributed to the low sensitivity reported in their study.

In this study, the ROC curve (Fig 2) and the summary statistics of diagnostic accuracy (Table 2) for LDCST showed that at a 30-minute cortisol cut-off value of 550 nmol/L, the LDCST had good sensitivity (97%) and specificity (78%). There was no advantage in using 580 nmol/L as the cut-off value, as it had a slightly lower specificity of 69%. No false negatives would have occurred if the 30-minute cut-off value had been raised to 600 nmol/L or beyond. At such high cut-off values, however, the specificity of the test would be too low, with the positive likelihood ratio of the test of approximately 1.5. Conversely, lowering the cut-off value to 450 nmol/L would give a specificity of 97%, but at the cost of reducing sensitivity to 47%, leading to a negative likelihood ratio of 0.54 and rendering the test inappropriate as a screening tool. We therefore recommend using 550 nmol/L as the optimal cut-off value for LDCST. At this cut-off value, the negative likelihood ratio of 0.04 is low enough to make the diagnosis of adrenocortical insufficiency highly unlikely when the test gives a negative result, although repeating the test may be considered worthwhile if clinical suspicion is very strong and the 30-minute cortisol level is 'borderline' (between 550 and 600 nmol/L). If LDCST gives a positive result, glucocorticoid replacement is indicated if the 30-minute cortisol level is lower than 400 nmol/L or the patient is symptomatic. If the 30-minute cortisol value lies between 400 and 550 nmol/L and the patient is asymptomatic, an ITT should be performed to exclude a false positive result.

A shortcoming of this study is that the two tests were not performed in a randomised sequence. All participants underwent a LDCST first, followed by ITT 4 to 7 days later. As the effects of ACTH are short lasting and the two tests were performed at least 4 days apart, no 'carry-over' effect from the ACTH given in LDCST was anticipated. To avoid potential systematic bias, however, ideally the sequence in which the two tests were performed would have been randomised.

The aim of this study was to evaluate the role of LDCST in the assessment of secondary adrenocortical insufficiency.

Renal/liver function tests	Other pituitary deficiency	30-minute cortisol level after low-dose corticotropin stimulation test (nmol/L)	Peak cortisol level during insulin tolerance test (nmol/L)
N¶/N	Nil	441	692
N/N	Gonadotrophin axis/ growth hormone axis	424	912
N/N	Nil	430	673
N/N	Gonadotrophin axis	417	794
N/N	Nil	495	612
Creatinine 205 μmol/L Normal liver function test	Nil	436	557
N/N	Gonadotrophin axis/ thyroid axis	536	588
N/N	Nil	513	584

False positive/ true negative	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
2/28	100	93	14.3	0
3/40	71	93	10.1	0.31
1/20	65	96	13.7	0.37
1/10	80	91	8.9	0.22
0/11	94	100	∞	0.06
0/53	50	100	∞	0.5
1/10	100	91	11.1	0
7/36	95	84	5.9	0.06
10/26	93	72	3.32	0.097
8/28	97	78	4.4	0.038
34/270	**90**	**89**		

It was not our aim to compare the LDCST with the 250 μg ACTH test, and the latter test was not performed in this study. We cannot therefore draw any conclusions about the superiority of LDCST over this test. Other studies in which these two tests were compared have shown that the 250 μg ACTH test was less sensitive than LDCST when the same 30-minute cortisol cut-off value was employed.[11,14-17] Some investigators have suggested that by simply using a higher cut-off cortisol value,[11,18,24] the sensitivity of the 250 μg test could be improved to that of LDCST. There is, however, no consensus as to what this value should be, or the best way to derive it. Other investigators have reported lower sensitivity with the 250 μg ACTH test even when higher cortisol cut-off values were used.[17]

Synthetic ACTH is only available in the form of 250 μg (1 ampoule). Special care is required in dilution to ensure delivery of ACTH 1 μg.[25] Also of note in this study is the clinical spectrum of patients included. There was a relatively high clinical suspicion of adrenocortical insufficiency in this patient group, with a pretest probability of 50%. Further evaluation of the utility of LDCST is required before clinical application to other patient groups is considered.

Conclusion

The LDCST, using a 30-minute cortisol cut-off value of 550 nmol/L, is a sensitive, safe, and convenient test for assessment of the hypothalamic-pituitary-adrenocortical axis. It can be used as a screening test for patients with suspected secondary adrenocortical insufficiency. The most cost-effective practice is to measure cortisol level at 30 minutes after administration of synthetic ACTH 1 μg.

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