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Original Article

Results confirming the efficacy of oral L-dopa on cortisol secretion in patients being evaluated for suspected growth hormone deficiency

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ABSTRACT

Objective: Adrenal insufficiency is a life-threatening disease and therefore, accurate diagnosis and prompt treatment are life-saving. The main purpose of this study was to retrospectively evaluate the serum cortisol levels measured during the L-dopa test in cases suspected GH deficiency and to compare the effect of L-dopa on cortisol secretion with the results of previous studies.

Method: Between January 2019 and January 2021, patients who underwent the L-dopa test for the evaluation of GH deficiency in our Pediatric Endocrinology Clinic and whose basal cortisol levels were measured at the baseline and at the 120th minutes of the test were included. The clinical, anthropometric, and laboratory data of the patients were obtained from the medical records.

Results: Eighty-five patients (38 girls, 47 boys) were included in the study. The mean age of the patients was 10.3 ± 3.5 years (range, 4.1 - 14.9 years). The mean serum cortisol level was 11.1 ± 3.6 µg/dL at baseline and 20.9 ± 3.8 µg/dL at 120th minutes (the mean cortisol increase was 9.8 ± 4.1 µg/dL). Cortisol response was adequate (> 18 µg / dL) in 76 cases (89.4%). Nausea/vomiting was observed in 53 (62.4%) of the patients during the L-dopa test. Peak cortisol responses of the cases with and without side effects were similar (20.9 ± 3.8; 20.8 ± 3.7; p = 0.945).

Conclusion: In conclusion, the L-dopa test is easy to apply, effective, and safe and can be performed to evaluate cortisol adequacy at least in patients being evaluated for suspected GH deficiency.

Keywords: Adrenal function, adrenal insufficiency, cortisol, cortisol deficiency, dopamine agonist, L-dopa

INTRODUCTION

Adrenal insufficiency is a life-threatening disease characterized by the lack of sufficient cortisol production in the adrenal glands, and accurate diagnosis and prompt treatment are life-saving.[1] Various pharmacological tests, including the insulin tolerance test (ITT), adrenocorticotropic hormone (ACTH) test, and glucagon tests, are widely used in the evaluation of the hypothalamic – pituitary – adrenal (HPA) axis.[2] Because of the possibility of a second pituitary hormone deficiency in patients with GH deficiency, adrenal insufficiency should be ruled out. ITT, ACTH, or glucagon test have been the most commonly used tools to measure cortisol secretion when evaluating the adrenal axis in patients with GH deficiency. Although ITT has been considered the gold standard, it is an unsafe test and serious neurological complications and even death have been reported.[2,3] On the other hand, the glucagon test has various disadvantages, including its long duration (180 minutes) and side effects such as vomiting and hypoglycemia.[4] In addition, although ACTH tests are effective, it does not allow us to evaluate GH secretion in addition to cortisol. Therefore, there is a need for an additional test to measure cortisol secretion in

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children with suspected growth deficiency. Some recent studies have suggested that L-dopa, which has been used for almost 50 years to measure GH deficiency, stimulates cortisol secretion and can be used in the diagnosis of adrenal insufficiency.[5,6] The results of our previous study investigating the effect of L-dopa on cortisol secretion in patients being evaluated for suspected GH deficiency confirmed the findings of previous studies.[7] Therefore, in our center, we started routinely using the L-dopa test to measure cortisol secretion in patients being evaluated for suspected GH deficiency. In addition to GH levels, we routinely measured serum cortisol levels at the baseline and 120th minutes in the patients who underwent the L-dopa test for suspected GH deficiency. In this study, we aimed to retrospectively evaluate the serum cortisol levels measured during the L-dopa test in cases suspected GH deficiency and to compare the effect of L-dopa on cortisol secretion with the results of previous studies.

MATERIAL AND METHODS

Between January 2019 and January 2021, patients who underwent the L-dopa test for the evaluation of GH deficiency in our pediatric endocrinology clinic and whose basal cortisol levels were measured at the baseline and at the 120th minutes of the test were included. All patients underwent a thorough physical examination and laboratory evaluation, including thyroid function tests to measure possible endocrine pathology. The clinical, anthropometric, and laboratory data of the patients were obtained from the medical records. Patients with chronic diseases (cardiovascular, gastrointestinal, and respiratory), a history of drug use (steroids and antipsychotics), endocrine pathology (Cushing syndrome and hypothyroidism), or suspected multiple pituitary hormone deficiency were excluded from the study. A Harpenden stadiometer with a sensitivity of 0.1 cm was used to measure height. Auxological evaluation was performed according to the Turkish National Growth Chart.[8] This study was conducted in accordance with the Declaration of Helsinki Ethical Principles, and approved by the Dr. Behçet Uz Children Hospital Clinical Research Ethics Committee (Protocol no:759 and Decision no: 2017/241). Each participant included in this study was informed about the scope of the study and written consent was obtained from the parents.

All experiments were performed as a routine diagnostic procedure in recumbent subjects in the morning between 7:30 and 8:00 a.m. after 10–12 h of fasting. The provocation tests were performed in the morning hours. On the morning of the study, subjects were not given breakfast, and a catheter was inserted into their antecubital vein; this system was kept open with saline. The patients were allowed to rest for 30 minutes before the stimulation test. For the test, a single oral dose of L-dopa (Madopar®, La Roche, Basel, Switzerland) was administered according to the weight of each subject (500 mg for children weighing > 30 kg, 250 mg for those weighing 15–30 kg, and 125 mg for those weighing < 15 kg). During the L-dopa test, serum GH levels were classically measured just before the administration of L-dopa and at the 30th, 60th, 90th, and 120th minutes, and in addition, serum cortisol levels were measured at the baseline and at the 120th minutes of the test. Side effects during the L-dopa test were recorded. All samples were analyzed immediately. Hormonal measurements were performed using electrochemiluminescence immunoassay procedures with the Cobas kit (Roche, Mannheim, Germany). Peak concentrations of cortisol exceeding 18 µg/ dL (496 mmol/L) were defined as an adequate response. A low-dose 1-microgram ACTH test was administered to the patients whose serum cortisol level was insufficient in the L-dopa test to investigate adrenal insufficiency.

Statistical analyses of the data were performed using the SPSS software package for Windows (Ver. 20.0; SPSS Inc., Chicago, IL, USA). The distribution of data was evaluated using the Kolmogorov-Smirnov test. For numerical comparisons, the Student's t-test or Mann-Whitney U tests was used to assess differences between the two groups according to the normal distribution of the measured parameters. Spearman's rho correlation was used to identify the associations between variables. Categorical data were expressed as frequency (%), while numerical data were expressed as mean ± standard deviation. In all statistical tests, *p*-values <0.05 were considered significant.

RESULTS

Eighty-five cases (38 females, 47 males) whose cortisol levels were measured during the L-dopa test were included in the study. The mean age of the cases was 10.3 ± 3.5 years (range, 4.1 - 14.9 years). According to Tanner staging, 54 of the cases were prepubertal and 31 were pubertal. The mean height SDS was -3.32 ± 0.84. The mean peak GH level was 5.8 ± 3.4 ng/mL.

Serum cortisol levels were 11.1 ± 3.6 µg/dL at baseline and 20.9 ± 3.8 µg/dL at 120th minutes (cortisol increase, 9.8 ± 4.1 µg/dL). The cortisol response was adequate (> 18 µg / dL) in 76 cases (89.4%) (Figure 1). In 9 cases with an inadequate cortisol response, ACTH test was performed and an adequate cortisol response was obtained, indicating that there was no patient with adrenal insufficiency among the subjects. The characteristics of 9 cases with a peak cortisol response of <18 µg/dL during the L-dopa test were presented in Table 1. Interestingly, three of the 9 cases with a peak cortisol level below 18 µg/dL at the 120th minute of the L-dopa test were found to have a baseline cortisol level above 10 µg/dL. Nausea/vomiting was observed in 53 (62.4%) of the patients during the L-dopa test. Peak cortisol

responses of cases with and without side effects were similar (20.9 ± 3.8; 20.8 ± 3.7, respectively; p = 0.945). On the other hand, no significant difference was found between the peak cortisol responses obtained during the L-dopa test of prepubertal and pubertal subjects (20.8 ± 3.7; 21.1 ± 3.8, respectively; p = 0.753). In addition, no significant correlation was found between age and peak cortisol (r = -0.065, p = 0.553).

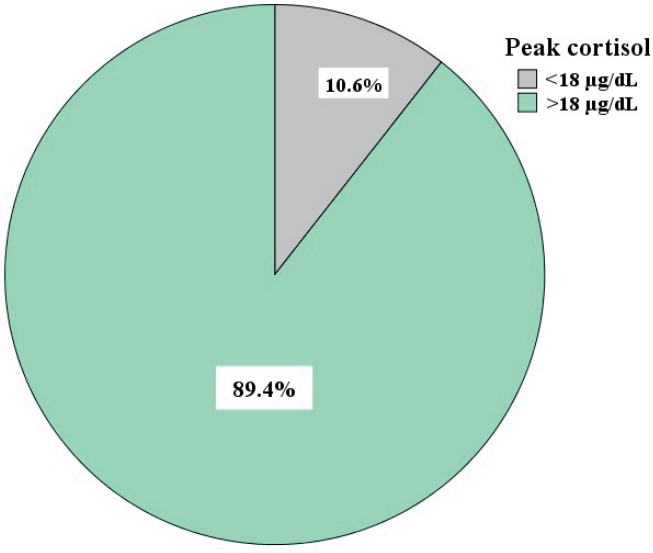

Figure 1. Determination of peak cortisol responses as adequate (>18 µg / dL) or insufficient (<18 µg / dL)

DISCUSSION

The effect of dopamine on cortisol secretion has been investigated for about 50 years. The first study was performed by King et al.[9] in 1959 in albino rats and showed that dopamine caused a significant increase in cortisol secretion. On the other hand, in the years following this study, various experimental studies conducted with a small number of subjects reported that intravenous or oral dopamine did not significantly increase serum cortisol secretion.[10-13] Subsequently, Stratakis et al.[14] demonstrated a moderate effect of dopamine on cortisol and ACTH secretion, and Philippi et al.[15] reported that dopamine had a significant stimulatory effect on cortisol secretion. Recently, in two different studies conducted by Marakaki et al., it was shown that 93% and 94.7% of cases had sufficient cortisol response with the L-dopa test.[5,6] However, the very small number of cases in our previous study and Marakaki's studies was the most important limitation. Similarly, in our previous study, the L-dopa test revealed that 26 of the 29 children (89.7%) had an adequate cortisol response (this rate was 79.3% in ITT, the gold standard test).[7] In the current study, in which the baseline and 120th-minute cortisol levels were evaluated in subjects who underwent the L-dopa test, the frequency of cases with an adequate cortisol response was found to be 89.4%. Considering the previous study results, the current study with a very high number of cases suggested that the stimulating effect of L-dopa on cortisol secretion is as effective as the gold standard test, ITT.

Dopamine, the dominant catecholamine neurotransmitter in the central nervous system, regulates various functions such as cognition, emotion, hunger/satiety, and the endocrine system (for example, prolactin suppression). While dopamine cannot

Table 1. The characteristics of 9 cases with a peak cortisol response of <18 µg/dL during the L-dopa test

Patient	Age (years)	Gender	L-dopa test		1-mcg ACTH test	
			Cortisol		Cortisol	
			Baseline (µg/dL)	120th minutes (µg/dL)	Baseline (µg/dL)	60th minutes (µg/dL)
1	5.1	Male	5.9	15.3	8.4	20.8
2	4.9	Male	7.9	16.8	9.8	19.9
3	11.5	Male	6.1	13.4	8.3	19.6
4	11.9	Female	8.1	14.9	16.8	26.3
5	14.0	Male	12.3	16.2	8.85	22.8
6	11.1	Female	5.4	9.4	7.92	24.5
7	14.3	Female	13.4	17.4	10.7	18.8
8	10.9	Female	7.9	8.9	9.2	21.1
9	4.3	Female	12.2	12.9	11.4	20.6

cross the blood-brain barrier directly, L-dopa, which is the precursor of dopamine, crosses the blood-brain barrier and binds to the dopamine receptor (known as D1-D5) in the central nervous system and displays its functions.[16] Administration of a dopamine agonist (bromocriptine) was demonstrated to increase the proopiomelanocortin (POMC) mRNA, a prohormone for adrenocorticotropic hormone (ACTH), concentration in the pituitary gland and hypothalamus.[17] Another study suggested that L-dopa is converted to norepinephrine by dopamine β-hydroxylase and, subsequently, stimulates the corticotropin releasing factor, which positively regulates the HPA axis.[18] The results of the experimental studies support that the dopamine agonist stimulates the HPA axis through various pathways and therefore increases the secretion of cortisol from the adrenal gland. In our previous study[7] and in the study by Marakaki et al.[5], ACTH levels were also shown to increase in correlation with serum cortisol responses during the L-dopa test, suggesting that the possible physiological mechanism of the cortisol-secreting effect of L-dopa is the increase in ACTH.

It has been demonstrated that the maturation of the HPA axis increases with age and with the progression of puberty, and as a result, cortisol secretion increases.[19,20] In the current study, similar to our previous study, no correlation was found between peak cortisol level and pubertal status or age. In addition, nausea/vomiting was observed in 53 (62.4%) of the patients during the L-dopa test, and peak cortisol responses were similar in patients with and without side effects. This finding was similar to the results of our previous study and the two studies of Marakaki et al.[5-7] Taken together, these findings suggest that the hypothesis that an increase in cortisol and ACTH secretion occurs as a result of side effects such as nausea/vomiting during the L-dopa test is not valid.

This study has some limitations. Considering the previous studies, it was shown that the peak cortisol response was obtained at the 120th minute in most of the cases during the L-dopa test.[5-7] Therefore, in our daily practice in our center, we measure serum cortisol at the baseline and at the 120th minute during the L-dopa test. Therefore, serum cortisol levels at these time-points were considered in this retrospective study. Since we did not measure cortisol levels at the 90th minute, we cannot exclude the negative impact of this on the peak cortisol responses. Furthermore, conditions affecting the bioavailability of oral L-dopa and thus peak cortisol levels were not considered in the current study.

In conclusion, the L-dopa test is easy to apply, effective, and safe and can be performed to evaluate cortisol adequacy at least in patients being evaluated for suspected GH deficiency. However, further studies are needed to evaluate its effectiveness in the diagnosis of adrenal insufficiency.

Ethical approval

This study has been approved by the Dr. Behçet Uz Children Hospital Clinical Research Ethics Committee (approval date 27/10/2022, number 759). Each participant included in this study was informed about the scope of the study and written consent was obtained from the parents.

Author contribution

Surgical and Medical Practices: TK, SA, BÖ, Concept: TK, SA, BÖ, Design: TK, SA, BÖ, Data Collection or Processing: TK, SA, ÖN Analysis or Interpretation: TK, ÖN, BÖ, Literature Search: SA, ÖN, Writing: SA, TK, BÖ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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