Hypothalamic-Pituitary-Adrenal Axis Recovery Following the 1-mg Overnight Dexamethasone Suppression Test in Healthy Volunteers

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Abstract

Background: The recovery of hypothalamic-pituitary-adrenal (HPA) axis suppression following pharmacological doses of various steroids has been studied previously. However, no study has been conducted using the more commonly used 1-mg dexamethasone in the overnight dexamethasone suppression test (ODST). Hence, we aimed at evaluating HPA axis recovery after the 1-mg ODST.

Objectives: This study aimed at investigating the pattern and time of recovery of the HPA axis following the 1-mg ODST in healthy subjects.

Methods: Ten healthy volunteers aged 18 - 40 years, BMI < 30 kg/m², with neither exposure to steroids nor interfering drugs were included. The 1-mg ODST was performed, and the adrenocorticotropic hormone (ACTH) and cortisol samples were withdrawn at regular intervals. The serum cortisol of < 1.8 µg/dL was considered as HPA axis suppression, whereas the cortisol value equal to or more than baseline was deemed as recovery.

Results: Cortisol and ACTH levels were suppressed in all subjects 9 hours following the 1-mg ODST. Although ACTH showed an early increase after 8 hours, the upsurge was noticed following 24 hours (mean ± SD, 34.42 ± 18 pg/mL). Later, cortisol accompanied ACTH, and both reached their baseline after 72 hours (mean ± SD, ACTH, 37.48 ± 12.44 pg/mL; cortisol, 8.45 ± 3.32 µg/dL). A small dip in ACTH and cortisol (mean ACTH, 23.84 pg/mL; mean cortisol, 2.3 µg/dL) was observed after 24 - 36 hours indicating the return of the diurnal rhythm before complete recovery.

Conclusions: The complete recovery of the HPA axis occurs only 72 hours following the 1-mg ODST. ACTH begins to recover as early as 8 hours after the maximal suppression and diurnal rhythm of ACTH and cortisol resume 24 to 36 hours later.

Keywords: Cortisol, Dexamethasone, Hypothalamic-Pituitary-Adrenal Axis, 1-mg Dexamethasone Suppression Test, Hypothalamic-Pituitary-Adrenal Axis Recovery

1. Background

Hypothalamic-pituitary-adrenal (HPA) axis suppression occurs most commonly due to exogenous steroid use (1). It is well known that the recovery of the HPA axis following glucocorticoid therapy depends on the type, route of administration, and a dose of the used drug and also the length of treatment. The degree of suppression and recovery of the HPA axis following the short- and long-term pharmacological doses of glucocorticoid therapy used in oncological and dermatological conditions has been widely studied (2-5). However, no study has yet been conducted using the 1-mg dexamethasone that is used more often in clinical practice to rule out hypercortisolism in the overnight dexamethasone suppression test (ODST). This test frequently is done on inpatients or as a part of preoperative investigations, and the patient is taken up for surgery within a couple of days. It may be worrisome that their HPA axis could remain suppressed when they undergo the stressful surgical procedure.

2. Objectives

Hence, we conducted this study to understand the pattern and time of recovery of the HPA axis following the 1-mg ODST.

3. Methods

3.1. Subjects

Ten healthy volunteers (6 men and 4 women) aged over 18 and younger than 40 years with a body mass in-
dex (BMI) of less than 30 kg/m² and no previous exposure to any forms of steroids or native medications, as well as drugs that could interfere with the HPA axis assessment (anti-tuberculous therapy, antiepileptics, oral contraceptive pills) were included. This research was a pilot study; therefore, only healthy volunteers (ten healthy subjects) were enrolled in this study. After obtaining informed consent, they were subjected to a detailed history and clinical examination. The ambulatory subjects were explained that they could perform their normal duties throughout the study period.

3.2. Methods

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Ethics Committee of Sri Ramachandra Medical College and Research Institute, Chennai, India. Fast sampling at 8 a.m. for serum cortisol and ACTH was done in all subjects at baseline. This was followed by the 1 mg ODST, where 1 mg dexamethasone tablet was given at 11 p.m., and the samples of ACTH and serum cortisol were measured on day 1 (8 a.m., 4 p.m.), day 2 (8 a.m., 4 p.m.), and day 3 (8 a.m.). Day 1 sample drawn at 8 a.m. was considered as 0 hour. A cut-off value of serum cortisol of < 1.8 mcg/dL was used to confirm HPA suppression. The recovery of the HPA axis was determined when the cortisol level following dexamethasone was equal to or greater than the baseline value. Additional samples were drawn if the serum cortisol level following ODST had not reached their baseline value. ACTH and cortisol were initially suppressed in all subjects, and one subject was studied until day 14 following ODST. This reconfirms our observation that ACTH recovery begins before cortisol recovery (6). Also, it was observed that the recovery of the adrenal component of the HPA response was delayed for 5 days, it has been shown that the peak cortisol response to physiologic ACTH release following hypoglycemia, as well as synthetic ACTH was reduced by 47% and 49%, respectively (6). Also, it was observed that the recovery of the adrenal component of the HPA axis was delayed for 5 days following prednisolone therapy. This reconfirms our observation that ACTH recovery begins before cortisol recovery (6). The return of diurnal rhythm occurs before the complete recovery of the HPA axis evidenced by the small dip in ACTH and cortisol levels between 24 and 36 hours. Although the exact mechanism remains unclear, we propose that it could be due to the negative feedback of cortisol.
Table 1. The Subjects’ Clinical and Biochemical Data (N = 10)\textsuperscript{a}

| Subject | Age, y | Sex | BMI (kg/m\textsuperscript{2}) | Baseline 0 hour | Cortisol | ACTH | 6 hours | Cortisol | ACTH | 24 hours | Cortisol | ACTH | 32 hours | Cortisol | ACTH | 48 hours | Cortisol | ACTH | 72 hours | Cortisol |
|---------|--------|-----|-----------------------------|----------------|----------|------|--------|----------|------|----------|----------|------|----------|----------|------|----------|----------|------|----------|----------|
| 1       | 39     | M   | 28.6                        | 44.9           | 6.3      | <10  | 0.6    | <10      | 0.5  | 30.2     | 2.1      | 26    | 3.1      | 5.3      | 35.2 |
| 2       | 36     | M   | 27.6                        | 22.9           | 10.9     | 0.9   | 20.6   | 0.4     | 44.6  | 5.1      | 28.8    | 2.7   | 19.6     | 9.8      | 34.4 |
| 3       | 38     | F   | 25.4                        | 20.9           | 6.7      | <10  | 0.4    | 0.4     | 10.2  | 0.5      | 10.1    | 0.5   | 18.1     | 0.1      | 107   |
| 4       | 27     | M   | 24.2                        | 13.3           | 11.9     | 0.9   | 20.6   | 0.4     | 44.6  | 5.1      | 28.8    | 2.7   | 19.6     | 9.8      | 34.4 |
| 5       | 34     | F   | 29                           | 22.9           | 0.5      | 10.8  | 0.8    | 24     | 0.4    | 24      | 1.9    | 26.3  | 2.0      | 28.5     | 14    |
| 6       | 32     | F   | 23.5                        | 22.9           | 0.5      | <10  | 0.5    | <10     | 0.3   | 50.1     | 7.7     | -     | -        | -        | -     |
| 7       | 29     | M   | 26.7                        | 18.2           | 0.7      | <10  | 0.8    | 15.3    | 0.5   | 42.9     | 5.1    | 10.1  | 4.0      | 41.5     | 7.8   |
| 8       | 36     | M   | 26.9                        | 10.8           | 9.1      | 12.7  | 0.5    | 19.3    | 3.7   | 24.8     | 5.9    | 12.6  | 4.7      | 59.2     | 8.2   |
| 9       | 36     | M   | 22.4                        | 32.4           | 12.2     | 22.3  | 0.4    | 28.4    | 0.3   | 54.4     | 3.2    | 33.8  | 0.6      | 107      | 11    |
| 10      | 38     | F   | 23.6                        | 22.4           | 3.4      | <10  | 0.5    | 10.2    | 0.3   | 13.1     | 3.3    | -     | -        | 21.3     | 3.7   |

\textsuperscript{a} ACTH is expressed in pg/mL and Cortisol is expressed in \(\mu\)g/dL.

Figure 1. Hypothalamic-Pituitary-Adrenal (HPA) axis recovery after the overnight dexamethasone suppression test in ten healthy volunteers.

Int J Endocrinol Metab. 2020; 18(2):e94908.
Figure 2. Change in adrenocorticotropic hormone (ACTH) levels between 48 and 72 hours during the recovery of Hypothalamic-Pituitary-Adrenal (HPA) axis in six healthy volunteers.

sone is the most potent among these drugs and is given at night to cause a greater suppression of ACTH, understanding about the recovery of the HPA axis with this drug is essential. The limitations of our study were the small sample size, less frequent sampling, and unavailability of the dexamethasone levels.

5.1. Conclusions

The complete recovery of the HPA axis occurs only 72 hours following the 1-mg ODST. ACTH recovery begins as early as 8 hours after the maximal suppression, and diurnal rhythm resumes after 36 hours.

Acknowledgments

The authors thank Sri Ramachandra University for the study grant and all the volunteers who participated in this study.

Footnotes

Authors’ Contribution: Study concept and design: Shrirama Mahadevan and Adlyne Reena Asirvatham; analysis and interpretation of data: Adlyne Reena Asirvatham and Karthik Balachandran; drafting of the manuscript: Adlyne Reena Asirvatham; critical revision of the manuscript for important intellectual content: Shrirama Mahadevan, Karthik Balachandran, Satish Kumar Balasubramaniam, and Adlyne Reena Asirvatham; statistical analysis: Karthik Balachandran.

Conflict of Interests: The authors have nothing to disclose.

Ethical Approval: The Institutional Ethics Committee of Sri Ramachandra University has approved this project titled “Estimation of the time taken for Hypothalamo-Pituitary-Adrenal axis recovery following overnight 1 mg dexamethasone suppression test” on 15.11.2016 with approval reference: IEC-N(16)/NOV/S6/78.

Funding/Support: This study was funded by Sri Ramachandra University under GATE project grant.

Patient Consent: The informed consent was signed by all participants.

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