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Tolerability of the Dexamethasone-Corticotropin Releasing Hormone Test in Major Depressive Disorder

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Abstract

Background—The dexamethasone-corticotropin releasing hormone (Dex-CRH) test may differentially predict which depressed patients will respond to antidepressant medication. However, a comprehensive analysis of the safety of this test in psychiatric patients has not been previously been performed.

Methods—We conducted a pooled analysis of depressed patients in four clinical studies. Observed and subjectively reported side effects in 454 patients were collected for 90 minutes following CRH administration. Pre-test electrocardiograms were available in 250 patients to assess cardiac safety. Descriptive statistics were performed to evaluate these safety data.

Results—Eight-six (18.9%) of all subjects experienced no side effects from the procedure. The mean number of side effects per subject was 1.4 ± 1.0 . The most frequent adverse events were: flushing (n=216, 47.6%), feeling of warmth (144, 31.7%), hyperpnea/tachypnea (108, 23.8%), palpitations (37, 8.1%), and tachycardia (28, 6.2%). Side effects were consistently mild and brief in duration. There were no serious adverse events.

Conclusion—The Dex-CRH test produces a mild, predictable side-effect profile, characterized by flushing, feelings of warmth, hyperpnea/tachypnea, palpitations, and tachycardia. These results provide reassurance that the Dex-CRH test is well tolerated in psychiatric patients.

Keywords

Cortisol; corticotropin releasing factor; predictor; adverse event; HPA axis; electrocardiogram

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INTRODUCTION

Major depressive disorder (MDD) affects approximately one in six adults during their lifetime (Kessler et al., 2003), but existing treatments induce remission in less than 50% of cases (Rush et al., 2008). Currently, there are no predictive tests that can be used to select the best treatment for a given patient. Biological tests predictive of treatment response would shorten the duration of time a patient may remain ill, and reduce likelihood of side effects.

One promising test for predicting treatment response in MDD is the dexamethasone-corticotropin releasing hormone (Dex-CRH) test (Holsboer et al., 1987). The Dex-CRH test combines the administration of dexamethasone at 11 pm the night before the assessment, with intravenously administered CRH the following afternoon at 3 pm. CRH is administered as a fixed dose of 100ug of human CRH or 1ug/kg of ovine CRH. Immediately prior to the CRH infusion, and at set intervals for the following 1-2 hours, plasma cortisol and ACTH concentrations are measured. In healthy subjects, the CRH is unable to or only mildly overrides the HPA-suppressing effects of dexamethasone and therefore subjects do not exhibit a substantial increase of cortisol or ACTH concentrations after CRH administration. In contrast, many patients with MDD demonstrate elevated plasma ACTH and cortisol concentrations in response to this test, presumably, as a result of an impaired signaling of the glucocorticoid receptor (GR) and of an increased secretion of the hypothalamic neuropeptides CRH and vasopressin (AVP) (Heuser et al., 1994). Reduced GR sensitivity attenuates the suppressive effects of dexamethasone at the pituitary and fails to inhibit CRH and AVP secretion from the paraventricular nuclei of the hypothalamus, which, in turn, enhances the stimulatory effects of the exogenous CRH in the combined Dex-CRH test (Holsboer, 2000). The test has also been studied in other psychiatric disorders, including bipolar disorder, post-traumatic stress disorder, panic disorder and alcohol dependence (Erhardt et al., 2006; Hundt et al., 2001; Muhtz et al., 2008).

HPA axis dysregulation during a major depressive episode, and its normalization after recovery, has been confirmed in several studies using the Dex-CRH test (Hatzinger et al., 2002; Heuser et al., 1994; Kunugi et al., 2006). MDD patients demonstrating sustained non-suppression of the HPA axis during the Dex-CRH test have a worse prognosis to respond to medication or psychotherapy treatments, compared to MDD patients with normalized Dex-CRH test profiles under therapy (Binder et al., 2009; Bschor et al., 2003; Ising et al. 2005). Dex-CRH test results may also predict the risk of depressive relapse (Aubry et al., 2007; Zobel et al., 1999).

Previous reports of the use of the Dex-CRH test have suggested that certain adverse events following CRH infusion are common, including flushing, tachypnea and tachycardia. These side-effects can be a direct result of peripheral CRH actions, as CRH receptors are present also in peripheral tissue including the myocardium (Wilkey and Davenport, 2004). Alternatively, these side effects may also be explained indirectly by a CRH dependent activation of the sympathetic nervous system, which can be mediated by CRH receptors located at sympathetic ganglia (Udelsman et al., 1986). Although EKG abnormalities have not been reported to be problematic in patients completing the Dex-CRH test, tachycardia resulting from the test presents a theoretical risk in patients with pre-existing cardiac disease.

To our knowledge, no serious adverse events (i.e. adverse events resulting or potentially resulting in death, hospitalization, or significant morbidity or disability) related to the Dex-CRH test in depressed patients have been reported previously. One potential serious adverse event requiring consideration is a possible anaphylactic reaction to the dexamethasone or

CRH. Sustained use of glucocorticoids, including dexamethasone, is associated with several important adverse effects, including osteoporosis, hyperglycemia, gastrointestinal ulceration, increased intraocular pressure, and a wide array of psychiatric symptoms (Roxane Laboratories, 2007).

In the early 1980s, two groups studying the low dose dexamethasone suppression test (DST) reported a temporal association of the test with subsequent suicide attempts (Asberg et al., 1981; Beck-Friis et al., 1981). Five of 83 inpatients who underwent the DST attempted suicide (one completed) within 48 hours of their dexamethasone dose. All 5 suicide attempters were women who had been considered at risk for suicide prior to the test, and two had prior suicide attempts. The authors of these reports did not assert there was a causal relationship between the DST and suicide attempts, but urged further evaluation of the test by other groups with larger DST datasets. Subsequently, two independent groups, which combined had studied the DST in 579 patients, found no association between the test and suicide attempts (Coryell, 1982; Kronfol et al., 1982).

Although prior studies reported minimal safety concerns in the use of the Dex-CRH test, the number of subjects in each study is relatively small. The increasing use of the Dex-CRH test in investigations of psychiatric illnesses require a greater understanding of the test's safety profile, so we undertook a descriptive analysis of the safety data from four studies.

METHODS AND MATERIALS

Patients and Study Descriptions

Data from four clinical studies with a total of 454 patients with MDD who completed a Dex-CRH test while depressed were retrospectively analyzed. Analysis of the tolerability and safety of the Dex-CRH test were not explicit goals in any of the studies, but tolerability and safety data were captured similarly in all studies. All studies were conducted in accord with the latest version of the Declaration of Helsinki. Three of the four studies were (PREdict, Conte, NARSAD) were performed at Emory University and were approved by the Emory University Institutional Review Board. The Munich Antidepressant Response Signature (MARS) study was approved by the local ethics committee of the Ludwig Maximilians University of Munich. Informed consent from participants was obtained after all the components of the study in which they were participating had been fully explained. In the MARS study sample, most patients were receiving medication treatment, excluding carbamazepine and lithium. For the remaining studies, all patients were drug-free at the time of testing. The four studies were:

Predictors of Response in Depression to Individual and Combined Treatments (PREdict); the Emory CIDAR—Data from 53 patients, ages 18-65, were gathered from this ongoing Emory University study of predictors of response to medication or psychotherapy in treatment-naïve MDD patients in a current major depressive episode. Salient inclusion and exclusion criteria include: 17-item Hamilton Depression Rating Scale (HDRS) score ≥ 18 ; lifetime history of OCD, bipolar disorder, or psychotic symptoms; substance dependence in the previous year, or substance abuse in the past 3 months.

Munich Antidepressant Response Signature Project (MARS): This study is a naturalistic longitudinal clinical evaluation of HPA axis variables as predictive factors for antidepressant treatment response in depression (Hennings et al., 2009). A total of 376 male and female inpatients, ages 18-75, in Southern Bavaria, Germany with a current MDE, either as part of MDD or Bipolar disorder underwent Dex-CRH testing. Severe medical conditions, lifetime alcohol dependence, illicit drug abuse depressive symptoms secondary to a medical or

neurological condition, and the presence of manic, hypomanic or mixed affective symptoms were exclusionary to participation in this study.

Emory Conte Center for the Neuroscience of Mental Disorders (CONTE): This study explored the relationship between childhood trauma and the development of depression and anxiety later in life (Heim et al., 2009). Eighty-five men and women, ages 21-45, were categorized by the presence or absence of a current major depressive episode, and presence or absence of childhood trauma (defined as abuse or neglect, or childhood loss prior to the age of 12). Of the 85 participants, 25 met criteria for current MDD and were included in the adverse event analysis. All participants with usable EKG data were included in the EKG analysis. Patients with any significant medical illness, current or lifetime psychotic symptoms or bipolar disorder, or a current eating disorder, illicit drug and/or alcohol abuse or current psychotropic medication were excluded.

Neurobiological and Hematological Correlates of Child Abuse in Adult Men (NARSAD): This study explored the long-term consequences of child abuse in adult men, focusing on endocrine, cardiovascular and behavioral systems. Adverse event data from the Dex-CRH test were not available for analysis, but twenty-six men, ages 18-55, with a diagnosis of current MDD had pre-test EKGs available for analysis. The inclusion/exclusion criteria were identical to the Conte Center study (Heim et al., 2008).

Dex-CRH Test

Dex-CRH testing procedures were similar in all trials, consisting of orally administered 1 or 1.5 mg of dexamethasone at 11 pm, followed by intravenous administration of CRH at 3 pm the following day in a hospital setting. The Emory PRedICT and MARS studies administered 100ug of human CRH; the Conte and NARSAD studies used 1 ug/kg of ovine CRH. Blood samples were subsequently collected at 5-30 minute intervals to measure HPA Axis hormone levels. Observed signs and spontaneously reported side effects were collected for 90 minutes following CRH administration.

Adverse Events

Elicitation of side effects was identified similarly in all projects; namely through the use of open-ended questions. Participants were asked during and after the infusion whether they noticed any changes in how they were feeling or if they had any uncomfortable experiences. In addition, physical signs including changes in vital signs or flushing were also assessed as potential adverse events. As part of the informed consent process, patients were advised of the side effects most frequently reported from Dex-CRH tests in prior studies. Raw adverse event data were converted into the Medical Dictionary for Regulatory Activities adverse event terms.

Electrocardiograms (EKGs)

Computerized readings of EKGs were grouped into categories of abnormalities. All available pre-test EKG findings from the four studies were evaluated. EKGs were considered “normal” if they identified no abnormality, or only an isolated right- or left-axis deviation with no other findings. Each individual abnormality on an EKG was reported as a separate finding, such that one patient’s EKG could contribute to multiple categories of abnormality. No intra-test or post-test EKGs were performed.

Statistical Analysis

Descriptive statistics were generated to report demographic information, diagnostic, EKG, and adverse event data, using SPSS version 16.0 for Windows.

RESULTS

Adverse Events

Adverse event data was available for 454 patients, who were predominantly women (n=239, 52.6%) and Caucasian (n=424, 93.4%), with a mean age 46.3 ± 14.1 years. Diagnoses were unipolar MDD (n=402, 88.5%) and bipolar disorder, current episode depressed (n=52, 11.5%). Psychotic features were present in 38 (8.4%).

Overall, 368 (81.1%) patients reported at least one adverse event, which resolved within minutes without further intervention. The mean number of AEs per patient was 1.4 ± 1.1 , with significantly higher reporting rates in the MARS (1.5 ± 1.0) versus the PRedICT (1.1 ± 1.2) and CONTE (1.1 ± 1.0) (F-Test 5.55, $p=.004$). Specific adverse events and their frequency are listed in Table 1. No serious adverse events were reported during the observation periods of the studies.

Electrocardiograms

Pre-test EKG data was available for 250 patients. Women comprised 93 (37.2%) of this sample, and the mean age was $40.5 (\pm 14.6)$ years. Study composition by race was: 168 (67.5%) Caucasian, 66 (26.5%) black, and 16 (6.0%) unknown or other. At least one EKG abnormality was detected in 163 (65.2%) of the sample. The specific EKG findings and their frequency is presented in Table 2.

DISCUSSION

Pooled data across three separate research study cohorts found the Dex-CRH test to be well tolerated, with no serious adverse events reported. A consistent side effect profile was identified, characterized by flushing, feeling of warmth, hyperpnea or tachypnea, palpitations and tachycardia, which all occurred in more than 5% of the sample. Although the rate of reported effects overall is high, the intensity was of the effects was low, and of brief duration. It is likely that some patients' anticipatory anxiety to the infusion contributes to the high reported adverse event rate, but the lack of a placebo control infusion prevents analysis of this potential contributing factor.

The MARS study had significantly higher rates of adverse events than the studies conducted at Emory University. We believe this difference most likely arises from the difference in depression severity levels of the study samples. The patients in the MARS study were all inpatients; whereas, the other three studies evaluated outpatients. Moreover, the MARS sample included patients with bipolar depression and psychotic depression. Greater depression severity may reflect more severely disrupted HPA function, making patients more sensitive to physiological changes associated with the CRH infusion.

Consistent with the larger analyses of the low-dose DST (Coryell, 1982; Kronfol et al., 1982), we found no indication of increased suicidality with administration of the Dex-CRH test. The most significant adverse event occurred in a patient with asthma, who experienced a possible asthma attack after CRH infusion, successfully treated with the patient's inhaled bronchodilator medication. The common experience of CRH-induced tachypnea may be interpreted by patients with asthma as an asthma attack, although there may be no reactive airway process actually occurring. CRH may be protective against asthma attacks through its central anti-inflammatory actions, with stimulation of the HPA axis and endogenous glucocorticoids. In a mouse model of asthma, CRH *deficiency* was associated with allergen-induced airway inflammation (Silverman et al., 2004). In humans, a small study of patients with nocturnal asthma suggested intravenous CRH administration improved forced expiratory flow volumes (Georges et al, 1998). In the periphery, however, CRH may

potentiate the immune response at sites of inflammation, possibly through inducing mast cell degranulation (Karalis et al., 1991; Theoharides et al., 1995). Even though preclinical and some clinical evidence suggests the Dex-CRH test may not pose a danger to patients with asthma, the adverse event in the MARS study suggests caution in conducting the Dex-CRH test in such patients.

The high overall rate of EKG abnormalities in the sample is consistent with other studies suggesting autonomic disturbance is common in patients with MDD, or arises as a consequence of antidepressant treatment (Koschke et al., 2009). Analysis of EKGs obtained in the 1-2 weeks prior to Dex-CRH testing in 250 patients indicated that mild disturbances on EKG did not pose a health risk to patients undergoing the Dex-CRH test. Although a few patients with more serious cardiac conditions, such as previous myocardial infarction or left bundle branch block did safely complete the test, too few patients with these EKG findings were included to definitively conclude the safety of the test in these patients. Moreover, this analysis was performed post-hoc, and there were no post-test EKGs to analyze. Thorough assessment of cardiac risk would have required post-test EKGs to determine whether the procedure produced any significant changes. Important EKG changes, such as lengthening of the QT interval, may be clinically silent, yet contribute to cardiac risk.

In conclusion, the Dex-CRH test is well-tolerated, with a predictable, short-duration side effect profile. Non-acute EKG abnormalities do not appear to represent a contra-indication to the test. If the Dex-CRH test does demonstrate utility in predicting response and relapse in MDD or other conditions, its application in general clinical settings would be reasonable.

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Table 1

Adverse events among depressed patients completing Dex-CRH test

| | PRedICT (N=53) | CONTE (N=25) | MARS (N=376) | TOTAL (N=454) |
|----------------------------|--------------------------|------------------------|------------------------|-------------------------|
| ADVERSE EVENT | | | | |
| NONE | 23 (43.4) | 9 (36.0) | 54 (14.4) | 86 (18.9) |
| Flushing | 10 (18.9) | 5 (20.0) | 201 (53.5) | 216 (47.6) |
| Feeling of Warmth | 7 (13.2) | 1 (4.0) | 136 (36.2) | 144 (31.7) |
| Hyperpnea/Tachypnea | 7 (13.2) | 1 (4.0) | 100 (26.6) | 108 (23.8) |
| Palpitations | 3 (5.7) | 2 (8.0) | 32 (8.5) | 37 (8.1) |
| Tachycardia | 4 (7.5) | 5 (20.0) | 19 (5.1) | 28 (6.2) |
| Dysgeusia | 1 (1.9) | 1 (4.0) | 11 (2.9) | 13 (2.9) |
| Paresthesia | 5 (9.4) | --- | 8 (2.1) | 11 (2.9) |
| Anxiety | 2 (3.8) | 1 (4.0) | 7 (1.9) | 10 (2.2) |
| Nausea | --- | 1 (4.0) | 9 (2.4) | 10 (2.2) |
| Chest Pressure | 1 (1.9) | 2 (8.0) | 5 (1.3) | 8 (1.8) |
| Chest Tightness | 2 (3.8) | --- | 5 (1.3) | 7 (1.5) |
| Dizziness | --- | 1 (4.0) | 6 (1.6) | 7 (1.5) |
| Lightheadedness | 2 (3.8) | 2 (8.0) | 3 (0.8) | 7 (1.5) |
| Feeling of Cold | 3 (5.7) | 2 (8.0) | 2 (0.5) | 7 (1.5) |
| Stomach/Esophageal | 1 (1.9) | --- | 5 (1.3) | 6 (1.3) |
| Discomfort Restlessness | 2 (3.8) | --- | 3 (0.8) | 5 (1.1) |

Table 2

Pre-Test EKG findings among depressed patients completing Dex-CRH test (N=250)

| EKG ABNORMALITY | Number with finding, (%) |
|---|---------------------------------|
| NONE | 87 (34.8) |
| <u>RATE</u> | |
| Sinus Bradycardia | 66 (26.4) |
| Sinus Tachycardia | 8 (3.2) |
| Marked Sinus Bradycardia | 3 (1.2) |
| Pacemaker | 1 (0.4) |
| <u>RHYTHM</u> | |
| Marked Sinus Arrhythmia | 3 (1.2) |
| Atrial Fibrillation | 2 (0.8) |
| Premature Atrial Complexes | 2 (0.8) |
| <u>CONDUCTION</u> | |
| Incomplete Right Bundle Branch Block | 21 (8.4) |
| 1 st Degree AV Block | 8 (3.2) |
| Prolonged QRS | 3 (1.2) |
| QT Prolongation | 2 (0.8) |
| Ventricular Conduction Delay | 2 (0.8) |
| Short PR Interval | 2 (0.8) |
| 2 nd Degree AV Block | 1 (0.4) |
| Complete Left Bundle Branch Block | 1 (0.4) |
| Poor R-wave Progression | 1 (0.4) |
| <u>REPOLARIZATION</u> | |
| Isolated T-wave abnormality | 20 (8.0) |
| Non-Specific Repolarization Disturbance | 13 (5.2) |
| Early Repolarization | 11 (4.4) |
| Non-specific ST Elevation | 7 (2.8) |
| ST Depression | 3 (1.2) |
| <u>ISCHEMIA</u> | |
| Possible Infarction | 3 (1.2) |
| Previous Infarction | 2 (0.8) |
| <u>STRUCTURE</u> | |
| Possible Left Ventricular Hypertrophy | 7 (2.8) |
| Left Ventricular Hypertrophy | 4 (1.6) |
| Possible Left Atrial Enlargement | 2 (0.8) |
| Right Heart Strain | 2 (0.8) |