Nalmefene Testing to Stimulate the Hypothalamic-Pituitary-Adrenal Axis in Patients at Risk for Pituitary Disease

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A. Introduction

The Hypothalamic-pituitary-adrenal (HPA) axis plays a vital role in the body's response to stress. Dysfunction at any site along this axis, if mild, can be asymptomatic in nonstressed individuals, but under stress, such as trauma, infection, or surgery, impairs the body's ability to mount an adequate cortisol response. This can result in significant morbidity and even mortality (1). Accurate assessment of HPA axis integrity is therefore of critical importance. The traditional gold standard for evaluating the HPA axis is the insulin hypoglycemia test (IHT). This test has several limitations: It is labor intensive, and contraindicated in elderly patients and patients with coronary artery disease or a history of seizures (2) A second test, the standard ACTH stimulation test, directly measures only the functional integrity of the adrenal glands, though it does indirectly assess hypothalamic and pituitary function as the adrenal glands depend on endogenous ACTH for its tropic effect. This test can detect severe deficiencies of cortisol, but often misses more mild or earlier cases (3). In addition, a recognized phenomenon of a window period after the onset of pituitary dysfunction during which the adrenal glands respond to exogenous ACTH prevents this test from differentiating between patients with normal adrenal function and those with early hypothalamic/pituitary dysfunction (4). Clearly, a better test for the evaluation of the HPA axis is needed.

This study proposes to evaluate stimulation of the HPA axis with the opiate antagonist nalmefene. Opioid receptors have a wide distribution throughout the brain, particularly in areas associated with neuroendocrine function such as the hypothalamus, and endogenous opioids have been shown to inhibit the release of ACTH and thus cortisol. Two opiate antagonists, naloxone and nalmefene, have been shown to stimulate the HPA axis. These drugs block the tonic inhibitory effect of endogenous opioids on central α1- adrenergic pathways, causing a release of corticotropin releasing hormone (CRH), a peptide hormone produced by the hypothalamus, and subsequently the release of ACTH from the anterior pituitary. ACTH released form the anterior pituitary then leads to the release of cortisol from the adrenal gland. Naloxone has been studied in patients at risk for pituitary disease (thus at risk for central adrenal insufficiency) showing good correlation with the IHT, the traditional gold standard (5,6). Several studies in healthy patients, however, have shown less reliable results, with naloxone failing to produce an ACTH and cortisol rise in all subjects (7,8). Nalmefene, which has a longer half-life than naloxone, is approved for intravenous use for narcotic overdose and postoperative respiratory depression, and has been shown to produce a greater stimulation of the HPA axis than naloxone. Preliminary studies in a small number of healthy subjects suggest that it may be useful as a stimulation test for the integrity of the HPA axis (9).

This study will assess the HPA axis in patients with pituitary disease with nalmefene stimulation testing and compare these results with IHT. If it correlates well with IHT, the gold standard for assessment of HPA axis integrity, nalmefene testing could be used to assess the HPA axis function and thus may be predictive of the body's ability to respond to stress.

B. Hypothesis

Nalmefene testing will compare to IHT, the gold standard for assessment of the integrity of the HPA axis, and will be an accurate and easily administered method of detecting subtle dysfunction in the HPA axis in patients at risk for hyopthalamic-piuitary dysfunction.

C. Methods

Study outcomes

- Measure nalmefene induced mean percent increase or decrease of ACTH and cortisol.
- Measure nalmefene induced peak ACTH and cortisol values.
- Compare the HPA response to nalmefene to that achieved with insulin induced hypoglycemia.

D. Study Design

36 Subjects with known hypothalamic-pituitary disease considered at risk for developing hypopituitarism will be studied. Subjects will first undergo a standard ACTH stimulation test to exclude patients with severe cortisol deficiency. If able to mount an adequate cortisol response, subjects will then undergo in a randomized order both testing with nalmefene and a standard insulin hypoglycemia test, at least one week apart. To control for gonadal steroid levels, female subjects will be studied only during days one through five of the menstrual cycle. A pregnancy test will be obtained from all women prior to enrollment in the study.

a. ACTH Stimulation test:

Subjects will first undergo standard ACTH stimulation testing with 250μg of Cortrosyn. This test is routinely conducted on patients who have undergone pituitary surgery as usual postoperative endocrine follow up. Subjects with a baseline morning cortisol of at least 5 μg/dl and a 60-minute post stimulation cortisol of at least 18 μg/dl will be a able to participate further in the study. At least one week after the ACTH stimulation testing subjects will undergo in a randomized order either a standard insulin induced hypoglycemia test (IHT) and then a nalmefene test or in the reverse order.

b. Nalmefene test:

Subjects will come in at 8am with no food or drink for 6 hours prior to the study initiation. A heparin lock will be inserted and at 9am baseline blood samples (10ml, or 2tsp) will be drawn every 15 minutes for cortisol and ACTH, with the last baseline sample drawn immediately before nalmefene administration. At 9:30am, 6mg of nalmefene will be injected intravenously, over 2 minutes. Blood samples will be drawn at times 15, 30, 45, 60, 90, and 120 minutes following nalmefene administration. Vital sign will be taken at baseline and every 15 minutes throughout the study period. A total of 100cc of blood will be drawn. Subjects will remain seated or supine during testing.

c. Insulin Hypoglycemia Test:

The IHT test will be performed after a 6 hour fast. After an angiocatheter is inserted, and with the patient lying supine, 0.15 units/kg of regular insulin will be administered IV. Blood sampling for glucose, ACTH, and cortisol will be obtained every 20 minutes for a total of 120 minutes. The test will be considered adequate if hypoglycemia of 40ng/dl or below is documented. IV glucose or orange juice by mouth will be given after the hypoglycemia target is achieved or if severe symptoms of hypoglycemia develop.

E. Study drug

Nalmefene (6-desoxy-6-methylenenaltrexone) is approved for intravenous use in humans for the treatment of opioid overdose and postoperative respiratory depression. In combined clinical trials, the administration of nalmefene to subjects with opioid overdose or respiratory depression has resulted in

tachycardia and hypertension in less than 5% of patients. None of these side effects were seen in healthy subjects receiving nalmefene for testing of the HPA axis (9,10)

F. Statistical Analysis

The effect of nalmefene on the hormones of the HPA axis will be analyzed by analysis of variance with appropriate post-hoc tests. The mean percent increase or decrease of hormone level compared to baseline will also be compared. The HPA response to nalmefene will be compared to that achieved with insulin-induced hypoglycemia. Patients with ACTH and cortisol responses less than 2 standard deviations below the mean will be considered abnormal. The concordance rate between the nalmefene test and the IHT will be determined using previously published normal criteria (11).

a. Sample Size

Based on Chi-square test analysis, 36 patients will be needed to show a 90% accuracy of nalmefene stimulation to detect mild pituitary dysfunction with a significance of $p < 0.05$ at a power of 80%.

G. Subjects and Recruitment

36 male and female subjects with known hypothalamic-pituitary disease will be studied. These patients have previously undergone pituitary surgery or radiation therapy and are a risk for hypopituitarism. Subjects will be recruited from the Endocrine clinic and from the Neuroendocrine and Pituitary Unit at the Columbia Presbyterian Hospital.

a. Inclusion criteria:

1. Adult men and women between the ages of 18-60
2. Subjects with a history of pituitary surgery
3. Subjects with a normal response to ACTH stimulation testing, with a baseline morning cortisol > 5 μg/dl and a 60 minute post stimulation > 18 μg/dl.

b. Exclusion criteria:

1. Subjects with a history of a seizure disorder, mental illness, coronary disease, or cerebrovascular disease.
2. Subjects with any abnormalities on vital sign testing.
3. Subjects with any history of narcotic drug use or any recent use of any narcotic analgesics.
4. Subjects with a history of alcohol or drug abuse.
5. Subjects taking glucocorticoids currently or within the past 6 months.
6. Subjects taking benzodiazepines, NSAIDS, or aspirin (these drugs have been shown to cause a falsely suppressed response to testing with naloxone).
7. Positive pregnancy or urine toxicology screen.

H. Confidentiality

All study data will be coded to safeguard the confidentiality of the study data and the identity of the subjects.

I.

J. Potential Risks

The risks of venipuncture/angiocath inserion include minimal discomfort and occasional bruising at the needle site. Rare complications include hematoma, superficial phlebitis, and cellulitis. The IV

injection of nalmefene can occasionally be associated with pain at the site, which is alleviated by slow infusion over two minutes. The administration of nalmefene to people with a history of opiate or narcotic drug use results in symptoms of narcotic withdrawal including sweating, nausea, sleepiness and possible fall in blood pressure. These subjects will be excluded from the study. The administration of nalmefene to subjects not taking narcotic drugs can infrequently produce symptoms suggestive of endogenous opioid withdrawal including nausea, chills, myalgias, mild depression, abdominal cramps, and joint pains. These symptoms are transient and rare, but monitoring for potential side effects will be conducted, all adverse events will be recorded, and the PI will be available to administer medical care as clinically appropriate.

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K. Potential Benefits

Potential benefits to society include a possible development of a clinically useful, safe, and easily administered test of the HPA axis.

L. Compensation

$50 will be paid to all subjects for completing each nalmefene test. Subjects will not receive additional compensation for ACTH or insulin hypoglycemia testing, as this is part of the routine evaluation for patients with pituitary disease at risk for HPA dysfunction.

M. Bibliography

1. Oelkers W. Adrenal Insufficiency. New Engl J Med 1996;335:1206-1212.
2. Biller SGaB. Laboratory Assessment of Adrenal Insufficiency. J Clin Endocrinol Metab 1994;79:923-93 1.
3. F. Ammari BI, E. Millward, MF Scanion. A Comparison Between Short ACTH and Insulin Stress Tests for Assessing Hypothalamic-Pituitary-Adrenal Function. Clin Endocrinol 1996;44:473-476.
4. A. I-1jortrup HK, J. Lindholm, P. Stentoft. Value of 30-minute Adrenocorticotropin (ACTH) Test in Demonstrating Hypothalaniic-Pitaitary-AdrenocorticaI Insufficiency after Acute ACTH Deprivation. J Clin Endocrinol Metab 1983;57:668-670.
5. LS Blevins AD, GS Wand. Naloxone-Induced Activation of the Hypothalamic-Pituitary-Adrenal Axis in Suspected Central Adrenal Insufficiency. Am J Med Sci 1994;308(3):167-170.
6. EJ Nye GH, JE Grice, CR Strakosch, DJ Torpy, RV Jackson. The Use of Naloxone for Investigating Disorders of the Hypothalamic-Pituitary-Adrenal Axis. The Endocrinologist 1999;9:161-182.
7. WJ Inder ME, MJ Evans, RA Donald. A Comparison of the Naloxone Test with Ovine CRH and Insulin Hypoglycernia in the Evaluation of the Hypothalariiic-Pituitary-AdrenaI Axis in Normal Man. Clin Endocrinol 1995;43:425-43 1.
8. AS McAllister DM, DR Hadden, PM Bell, H Leslie, B Sheridan, AB Atkinson. A Comparison of the Naloxone Test with the Insulin Stress Test in Patients Following Transphenoidal Surgery. Clin Endocrinol 1999;50:261-265.
9. JH Schluger AH, L Borg, M Porter, S Maniar, M Gunduz, G Perret, A King, MJ Kreek. Nalmefene Causes Greater Hypothalamic-Pituitary Adrenal Axis Activation than Naloxone in Normal

Volunteers: Implications for the Treatment of Alcoholism. Alcohol Clin Exp Res 1998;22(7):1430-1436.
10. Product Information: REVEX (R), nalmefene. In:. New Providence, NJ: Baxter Pharmaceutical Products; 1999.
11. EJ Erturk CJ, AL Barkan. Evaluation of the Integrity of the Hypothalarnic-Pituitary-Adrenal Axis by Insulin Hypoglycernia Test. J Clin Endocrinol Metab 1998;83:2350-2354.