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Project Number: 99-CH-0055

Drug/Device:
[^{18}F]- L-3,4-dihydroxyphenylalanine (^{18}F-DOPA), IND# 35513;
IND Sponsor: Dr. Peter Herscovitch
mifepristone, IND#70795; IND Sponsor: Laboratoire HRA-Pharma

Revision Date: July 6, 2017

Subject: New Imaging Modalities in the Evaluation of Patients with Ectopic Cushing Syndrome

Identifying Words: PET, [^{18}F]-DOPA, Pentetreotide, Octreotide, ACTH

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***Investigators with this designation will obtain informed consent for this protocol**

Estimated Duration of Study: 15 years

Subjects of Study:	**N**	**Age Range**
Cushing syndrome, for screening	202	18-90
Of these patients, for PET and Octreoscan	100	18-90

Project uses ionizing radiation? Yes. Radiation use is indicated for research. NIH Radiation Safety Committee has approved this use (rad authorization 1781C).

Project involves use of Durable Power of Attorney? No

Off-Site Project? No

Multi-Institutional Project? No**PRECIS**

Between 10% and 20% of patients with hypercortisolism (Cushing syndrome) have ectopic production of adrenocorticotropin hormone (ACTH) that causes cortisol excess. In approximately 50% of these patients, the source of ACTH cannot be found despite very detailed and extensive examination including imaging studies such as computed tomography scanning, magnetic resonance imaging, and octreotide scan (Octreoscan) using the standard dose of indium- 111 pentetreotide ([^{111}In-DTPA-D-Phe]-pentetreotide). The sensitivity and specificity of these imaging studies depends on anatomic alterations and/or the dose and adequate uptake of radiopharmaceutical. In contrast, positron emission tomography (PET) has the ability to detect pathologic tissue based on physiologic and biochemical processes within the abnormal tissue. This protocol tests whether [^{18}F]-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) can be used to localize successfully the source of ectopic ACTH production. In addition the study examines whether administration of the glucocorticoid antagonist mifepristone can improve the sensitivity of the standard dose Octreocan. Eligible patients participating in this arm of the study will have a second standard dose

dose Octreoscan. Eligible patients participating in this arm of the study will have a second standard dose scan. Others will receive a higher dose octreoscan instead.

INTRODUCTION

Cushing's syndrome is an endocrine disorder caused by excessive production of glucocorticoids. In 10%-20% of patients this syndrome results from ectopic production of ACTH and very rarely from ectopic CRH production (1-6). Small cell carcinoma of the lung, islet cell tumor of the pancreas, medullary thyroid cancer, pheochromocytoma, and foregut carcinoid tumors are the most common sources of ACTH production (1,2,5,7). The mean age at diagnosis in patients with ectopic ACTH production is 40 years and the male-female ratio is almost 1:1 (1,8). The ectopic source of ACTH production cannot be found in 50% of patients despite aggressive, extensive, and expensive testing (9,10). These patients are at high risk of death due to sepsis, hypertension, gastrointestinal pathology, and metastatic dissemination (8,11). More than 50% of patients with ectopic ACTH production cannot be treated surgically or fail medical therapy and therefore, they finally undergo adrenalectomy with life-long hormone replacement therapy (8). However, if the source of ectopic ACTH production is found before the tumor metastasizes, resection is usually curative. Thus, the ability to image primary and/or metastatic lesions has proved to be the key to successful treatment. Conventional imaging is generally performed with computerized tomography (CT) and magnetic resonance imaging (MRI) of the chest and abdomen. ^{123}I-Metaiodobenzylguanidine (MIBG) is taken up by adrenal tissue and pheochromocytomas and may be useful in identifying this source of ectopic ACTH secretion. As discussed below, other modalities, including somatostatin receptor scintigraphy and various positron emission tomography (PET) ligands, also may be useful in the localization of these tumors.

Somatostatin receptor scintigraphy using [^{111}In-DTPA-D-Phe]-pentetreotide (Octreoscan, OCT), an analog of somatostatin, may identify gastroenteropancreatic tumors, carcinoids, and medullary thyroid carcinomas, all of which express somatostatin receptors (12). The conventional 6 mCi dose of OCT has been reported to localize ectopic ACTH production, at NIH and elsewhere (12-14). De Herder et al. reported a sensitivity of 78% for Octreoscan in patients with ectopic ACTH production (15). However, at NIH, our experience with somatostatin receptor scintigraphy using the conventional dose of 6 mCi of [^{111}In-DTPA-D-Phe]-pentetreotide has not been as promising. Detectability of lesions in scintigraphic studies depends not only on the size of the lesion but also on the amount of radioactivity in that lesion. Thus, in the original version of this protocol, we investigated whether a higher dose of radiopharmaceutical could lead to higher concentrations in a lesion and better visualization. In thyroid cancer, it is known that higher doses of ^{131}I can detect more lesions than lower doses. Furthermore, investigators using high doses of [^{111}In-DTPA-D-Phe]-pentetreotide for therapy (180 mCi) have seen more lesions on patients' post therapy scans as compared to their diagnostic scans (16). Analysis of 27 patients with surgically-proven ectopic ACTH-secreting tumors showed a 59% sensitivity for the "low dose" (6 mCi, L-OCT). In patients who had negative L-OCT, "high dose" (18 mCi, H-OCT) had an additional 58% (7/12 patients) sensitivity (17). As a result, the project was amended in 2006 to consider the high dose Octreoscan a medically-indicated test.

However, H-OCT delivers a substantial radiation dose, particularly when coupled with the L-OCT as is done here. In particular, the bladder receives high dose because these radiopharmaceuticals are excreted by the kidneys. (See later: concern about radiation).
Thus, while the benefit-to-risk ratio has been considered acceptable because of improved localization and the high morbidity and mortality experienced by patients with this disease, a lower radiation dose would be preferable. To this end, we propose evaluation of whether the antiglucocorticoid mifepristone can improve L-OCT sensitivity in patients with active hypercortisolism. ^{111}In-DTPA-D-Phe]-pentetreotide binds primarily to the somatostatin receptors subtypes (sst) 2 and 5. There is a large variability in functional sst2 receptor expression in these tumors (18), which may account for failure of OCT detection of tumors. One explanation for this variability is that glucocorticoids can directly down-regulate the expression of sst2 in neuroendocrine cells *in vitro* (19-20). If this is the case *in vivo*, antagonism of glucocorticoid action would be expected to relieve this down-regulation, and possibly allow for conversion of a negative OCT to a positive study. Two patients treated with mifepristone at the NIH and in the Netherlands, who converted from a negative to a positive scan, generated this hypothesis (22). However, the interval between the scans was from 2 – 12 months. To test this hypothesis formally, we will administer mifepristone to individuals whose initial L-OCT is negative, and will obtain a second L-OCT after ten days of mifepristone 600 mg daily. This dose is expected to antagonize most glucocorticoid effect in patients with ectopic ACTH secretion.

PET is a method of imaging disease based on the uptake and metabolism of a specific radiopharmaceutical by various tissues. [^{18}F]-Fluorodeoxyglucose (FDG) PET has been used for years in evaluating brain anatomical and functional abnormalities and more recently, in tumor localization (22). Several studies have shown that malignant lesions (e.g. lung, bone, and colorectal cancers, lymphoma) demonstrate elevated glycolysis when compared to normal tissue (23). In our previous review of results from this project (24) as well as in our recent analysis (17), the sensitivity of the test in patients with found tumors is 64% (7/11) and 47% (7/15) when all patients were considered (including occult tumor patients). However, FDG PET did not detect (or suggest) any tumors that were not identified by CT and/or MRI.

Because of the inability of FDG PET to detect otherwise occult tumors, we explored the availability of other ligands. Neuroendocrine tumors such as foregut carcinoids have been classified as APUDomas based on demonstration of amine precursor uptake and decarboxylation (25). In particular, tryptophan is taken up and 5-hydroxylated to 5-hydroxy-tryptophan (5-HTP). Carcinoid tumors that express the enzyme aromatic amino acid decarboxylase (usually the mid-gut carcinoids) can decarboxylate 5-HTP to serotonin (5-hydroxytryptamine or 5-HT). Sundin and colleagues demonstrated that these tumors take up and retain [^{11}C]-5-HTP, allowing visualization via PET (26). Similarly, the tumors take up and decarboxylate L-3,4-dihydroxyphenylalanine (DOPA) (27). The activity of L-DOPA decarboxylase is increased in these tumors (28-30). In a series of small studies, [^{18}F]-DOPA PET (F-DOPA PET) or [^{11}C]-DOPA PET had a sensitivity for pancreatic neuroendocrine tumors, gastrointestinal carcinoids, other carcinoids, melanoma, small cell lung cancer, pheochromocytoma, glomus tumor, and medullary thyroid cancer of 50 to 85% (31-38). Although ^{11}C-5-HTP is not available as a ligand at the Clinical Center, F-DOPA is available. Since F-DOPA PET potentially has a better sensitivity than FDG PET, we discontinued the research evaluation of FDG PET and substituted F-DOPA PET.

We found that F-DOPA PET substantiated a lesion seen on CT and/or MRI scan in 6 of 11 patients, including some with questionable results on conventional imaging. We amended the protocol in 2008 to administer carbidopa, 200 mg, one hour before the study. Dr. Pacak has found that this strategy improves tumor detection of pheochromocytoma, presumably by inhibiting decarboxylation of the tracer. This amendment will now allow us to perform FDOPA PET/CT, which was not available previously.

The project was amended in 2004 regarding the routine chest MRI scans. We initially obtained images on a 0.5 T magnet using, using STIR, T1 and T2 images. Subsequently a 1.5 T magnet replaced the lower strength magnet and STIR images were not obtained. Recently a 3.0 T magnet has become available with image acquisition gated to the EKG R-R interval so that artifact from cardiac motion is reduced. Our collaborator Dr. Gharib has performed T1 and T2 sequences using this approach with excellent resolution of mediastinal and chest structures. Increased strength of magnetic field compared to conventional 1.5T MRI allows for a stronger signal and therefore improved signal to noise ratio. Free breathing techniques are used to avoid breath holding, which may be difficult for those patients with volume overload. The combination of higher signal and decreased motion artifacts should significantly improve resolution allowing for better delineation of small lesions that may be responsible for ectopic ACTH production. To test this, we have added these sequences.

We wish to clarify the use of chest CT scans, as the available modalities have changed. A “surgical chest protocol CT” (which involves thin (1-2mm) cuts throughout the thorax) will be obtained at each visit. For the initial imaging, gated “cardiac CT” will be obtained as well to look for retrocardiac lesions that can be obscured by non-gated routine CT. However, because of the amount of radiation, we will obtain this scan only at the initial visit, unless there is a subsequent clinical suspicion of a retrocardiac lesion.

OBJECTIVES

Specific questions to be addressed:

F-DOPA PET/CT

(a) Compared to other imaging techniques, is the sensitivity and specificity of F-DOPA PET/CT higher in detecting the source of ectopic ACTH production in patients with known and unknown tumor localization?

(b) Does a correlation exist between F-DOPA uptake and the type of tumor, its size and proliferative activity?

Octreoscan

(c) Can the administration of mifepristone, 600 mg daily for 10 days, convert a negative standard 6 mCi OCT (L-OCT) to a subsequent positive result?

MRI

(d) Does gated chest MRI detect more lesions than routine MRI?

STUDY DESIGN AND METHODS

Standard Medical Evaluation of Cushing Syndrome

We will evaluate patients at the Clinical Center on an inpatient ward. Each subject will undergo a complete medical history, physical examination, and chemical screening tests, including acute care panel, liver function tests, thyroid function tests, complete blood count, plasma ACTH levels (30 ml of blood), and urine free cortisol. Patients also undergo measurement of diurnal cortisol in blood and saliva to confirm the diagnosis of Cushing syndrome (20 ml of blood). This is followed by a CRH stimulation test (30 ml of blood), inferior petrosal sinus sampling (IPSS; 90 ml of blood) and 8 mg overnight dexamethasone suppression test (10 ml of blood). Patients undergo MRI before IPSS: those with a mass greater than 6 mm diameter may not need IPSS, if CRH and dexamethasone suppression tests are compatible with Cushing's disease. All of these tests are performed as part of the standard evaluation of Cushing syndrome.

The initial diagnostic evaluation lasts up to 14 days. Where not limited by medical or social concerns, and where guesthouse accommodation is available, it may be performed in the outpatient/day hospital areas except for overnight stays associated with diurnal sampling. Patients whose results are consistent with Cushing's disease will be referred for transsphenoidal surgery, and will not undergo the imaging studies described below.

Patients whose evaluation indicates ectopic ACTH secretion (generally, lack of response to CRH, dexamethasone and lack of central to peripheral ACTH gradient on IPSS) will undergo standard, medically-indicated, imaging studies for localization of the tumor, including CT (neck, chest, abdomen, and pelvis), 1.5 T MRI (neck, chest, abdomen, and pelvis), and 6 mCI standard Octreoscan (L-OCT). Women will undergo a serum pregnancy test within 24 hrs before administration of any isotope.

Patients without active hypercortisolism in whom the standard Octreoscan is negative (or those ineligible for the mifepristone study) will undergo H-OCT. Because of interference we will wait at least one week after dosing a low dose Octreoscan before doing a H-OCT. The IRB previously agreed that this would be a medically indicated procedure in these patients. However, because it adds significantly to the cumulative radiation exposure, we have decided to limit this to three scans at intervals of at least one year.

The duration of standard imaging studies is about 10-15 minutes for either CT of the neck, chest, abdomen, or pelvis and 1-2 hours for either MRI of the pituitary, chest, abdomen, or pelvis, and 1-3 hours for Octreoscan (see below).

Research Procedures

Eligible patients with active hypercortisolism will receive the mifepristone-L-OCT combination as a research study (see below). Patients will undergo F-DOPA PET/CT as a research study, up to two studies with an interval of at least 12 months. Patients may undergo imaging before or after treatment of ectopic Cushing syndrome (if they have evidence of active ectopic ACTH secretion). Because of interference and to allow for administration of mifepristone, we will wait at least ten days after dosing a low dose Octreoscan before doing a second L-OCT. A gated chest MRI will be obtained using a 3 Tesla magnet with T1 and T2 sequences. Blood will be collected into one heparin and serum tube and an aliquot of urine will be retained for additional clinical or future research studies related to hypercortisolism. As an example, we previously studied the utility of pro-calcitonin using research samples collected under another protocol (39). Patients will be asked to consent to the future use of tumor samples. If they consent to such use, samples may be used in the future, with identifiers, for studies not described here, without obtaining new informed consent. Only studies related to Cushing's syndrome or the biology of tumors would be undertaken.

F-DOPA PET/CT procedures

The research team is responsible for ensuring that PET-specific regulations and procedures are followed. Patients are studied in the PET Department scanning facility at the Clinical Center after a minimum of 6 hours fasting. A plastic catheter is inserted into an arm vein. Patients receive carbidopa, 200 mg, orally 60 minutes before the scheduled injection of F-DOPA.

The Pet Department's new PET/CT scanner has higher resolution and sensitivity than the older GE Advance instruments and allows us to perform a low dose CT for attenuation correction and localization. The F-DOPA dose (12 mCi) is injected intravenously over approximately 2 minutes. During the infusion, the patient is instructed to rest quietly. After a 30 min. uptake period, patients undergo a low dose attenuation CT, followed by imaging of the pelvis through the pituitary.
The F-DOPA PET scan lasts up to ~2 hours. Patients having problems controlling their urine may need to use a Foley or condom catheter for approximately 12 hours after the injection of F-DOPA.

Octreoscan procedure

Patients are studied in the Nuclear Medicine scanning facility at the Clinical Center. Patients are ncouraged to hydrate themselves well before and after administration of [^{111}In-DTPA-D-Phe]-pentetreotide to aid in renal elimination of unbound material.

The patient is injected intravenously with approximately 6mCi (L-OCT) or 18 mCi [^{111}In-DTPA-D-Phe]-pentetreotide (H-OCT) in the Department of Nuclear Medicine and is imaged 4 and 24 hours later. Whole body and SPECT/CT images are obtained. For the clinical Octreoscans, additional delayed images may be obtained if necessary. Octreotide imaging takes 1-3 hours each day, depending on the clinical situation. Patients having problems controlling their urine may need to use a Foley or condom catheter for approximately 24 hours after the injection of Octreotide. Some patients will be administered a laxative after the first day of imaging to clear bowel contents, as clinically indicated.

For the mifepristone study, mifepristone will be administered at a total daily dose of 600 mg (given as one 200 mg tablet tid, per os) starting 10 days before a second research L-OCT is performed. It will be given in the morning (before breakfast), middle of the day (either immediately before lunch for subjects who have late lunch or 2 hours after lunch for subjects who have an early lunch), and evening (either immediately before dinner for subjects who have late dinner or 2 hours after dinner for subjects who have an early dinner). Blood (8 ml) will be drawn on the morning of the second scan, and will be stored for possible measurement of mifepristone. No other medical treatment for hypercortisolism will be given during this time. A research L-OCT will then be performed.

The research L OCT scan will be performed in the same manner as the clinical study, except that SPECT/CT of any one area will only be performed up to 2 times. All other SPECT studies of the area will be performed without CT. No clinical H-OCT study will be performed on these patients within one year of the research L OCT study.

Evaluation and treatment at the conclusion of imaging episodes

The investigators will review the results of all imaging studies at the end of each admission. Imaging results will be correlated; as is typical in standard medical care, we will not blind the reader of any conventional images to other results. However, the F-DOPA PET/CT, studies will be read without knowledge of the results of conventional MRI and CT studies. If the conventional imaging studies localize a possible tumor, the patient will undergo surgical resection, probably during a subsequent admission. If the conventional imaging studies are equivocal, or if only the research studies suggest a tumor, additional studies will be performed as clinically indicated. These studies may include repeat CT scan focused on the area of concern, venous sampling for ACTH measurement in chest or abdominal vessels, ultrasound examination, bone scan, MIBG scan, fine needle biopsy or other tests. The patient will not undergo surgery unless additional studies reveal a mass. Thus, at the conclusion of each episode of evaluation (and possible treatment), some patients with positive imaging will have surgical confirmation of the source of ectopic ACTH secretion. All others will be non-localized. These patients will receive treatment for hypercortisolism (usually medical, but adrenalectomy may be chosen), and will return to the Clinical Center to have repeated CT and MRI imaging (every 6-12 months) and repeated F-DOPA

Clinical Center to have repeated CT and MRI imaging (every 6-12 months) and repeated F-DOPA PET/CT and OCT (every 12 months).

If Cushing syndrome recurs or if patients are not cured by initial resection, patients are offered re-evaluation to localize any residual tumor or recurrence. In that case, all clinical, biochemical, and imaging tests may be repeated similar to the initial visit. Upon completion of the study, the patients are returned to the care of their referring physician.

Concern about radiation dose

Patients receive radiation exposure with the medically indicated dedicated CT scans as well as with the low-dose CT scans used for attenuation correction and co-registration with PET and Octreoscans. The low and high dose octreoscans and the PET scans also deliver radiation. The kidneys excrete these radiopharmaceuticals. As a result, the bladder receives a higher dose of radiation than other tissues. At the doses potentially reached with the combination of L OCT plus H OCT, there may be a slight increased risk of urinary bladder cancer. In patients receiving another radioisotope (I-131) in amounts that give significantly higher doses to the urinary bladder, results have been variable. One major study showed no significant increased risk whereas another showed a small increased risk of death from urinary bladder cancer (44,45). This latter study showed that approximately 2 out of 1000 people will die from bladder cancer over a 50 year lifetime after a dose of 100 rem to their urinary bladder. The dose to the urinary bladder in from the combination of a clinical L OCT, clinical H OCT with their accompanying attenuation CT scans is less than this. The risk of fatal bladder cancer in the general population is 5 in 1,000. Therefore, patients participating in this protocol and/or the alternative proposed clinical scans may have an increased risk of a fatal bladder cancer.

In consideration of these issues, exposure will be limited as follows: F-DOPA or a larger dose of [^{111}In-DTPA-D-Phe]-pentetreotide can be repeated in patients with recurrent or persistent disease, but not until twelve months after the last PET or Octreoscan. No patient will undergo a third F-DOPA. Patients who previously received FDG PET may undergo two F-DOPA PET scans. A total of up to three H-OCT scans will be performed in any ectopic ACTH patient followed at the NIH. Therefore, in those who undergo the L-OCT with mifepristone on this protocol, only two H-OCT scans will be allowed.

PATIENT SELECTION

Inclusions

All eligible patients are invited to participate in this protocol. Patients are adults with possible ectopic Cushing syndrome. Since both men and women are affected with ectopic Cushing syndrome, both sexes are studied. All ethnic and racial groups are at risk and will be included. Patients must be willing to return to NIH for follow-up studies.

Exclusions

• Pregnant or lactating women. A pregnancy test is performed in women of childbearing potential (up to age 55) unless they have a history of hysterectomy.

• Children (age less than 18) are excluded. Because ectopic ACTH secretion is rare in this age group, the likelihood of benefit is less and does not balance the risk of radiation.

• Patients taking medications that alter CYP3A4 activity will not be eligible for the mifepristone study, since this P450 system metabolizes mifepristone. Such participants would receive a clinical H-OCT instead, if the L-OCT were negative. Patients with hypokalemia (K < 3.5 mEq/L), despite medical therapy with replacement or mineralocorticoid antagonists will also be excluded from the mifepristone studies.

The presence of

• severe active infection.

• clinically significantly impaired cardiovascular (e.g. history of abnormally low ejection fraction, the presence of moderate pulmonary fluid overload, and blood pressure over 190/100), abnormal coagulation in the absence of medically-indicated treatment (PT and PTT elevated by 30% above the normal values), hematopoietic (hematocrit less than 30%, hemoglobin below 10 g/dl, white count below 3000 K/UL, and platelets below 100,000 K/mm^3), hepatic (liver enzymes elevated by 3-fold above normal values), or renal function (plasma creatinine level over 2.0)

function (plasma creatinine level over 2.0).

• impaired mental capacity or markedly abnormal psychiatric evaluation that precludes informed consent.

• body weight over 136 kg, which is the limit for the tables used in the scanning areas.

• combined blood withdrawal during the six weeks preceding the study greater 450 ml.

• known allergy to [^{111}In-DTPA-D-Phe]-pentetreotide or other somatostatin analogues.

• strong evidence for Cushing's disease. This includes those with a central to peripheral ACTH gradient during IPSS or a lesion on pituitary MRI. We anticipate that these exclusion criteria will increase the ratio of patients with ectopic ACTH syndrome to those with Cushing's disease from the usual 1: 8 to 1: 2, thus we would accrue 3 patients to identify one with ectopic ACTH secretion.

ANALYSIS OF THE STUDY

Justification of the number of subjects
The IRB previously approved an accrual ceiling of 202 for the high dose octreoscan component. That component is no longer a part of the protocol. Eighty-nine patients have enrolled in the protocol. F-DOPA PET was positive in 8 of 17 patients with known tumors and high dose Octreoscan was positive in 7 of 12.

Given these encouraging results, we propose performing F-DOPA in a total of at least 30 patients. The current results imply an estimated success rate of about 55% for each modality; the plausible range for the true success rate ranges from about 26 to 80% using a 95% confidence interval, a very broad range. Studying a total of 30 patients will allow us the possibility of precluding a true success rate of under 20% (with 95% confidence) if we were to see no additional successes. If there are additional successes in the additional patients the confidence interval for what the true probability of success could be will still be fairly broad. Since limited patients have been evaluated using F-DOPA, we ask that the overall accrual ceiling remain intact and that it be altered based on annual reports of the results. Additionally, we have essentially no data on which to base a sample size calculation for the mifepristone study, and would re-calculate accrual limits when such data are available.

Data Collection and Evaluation

Staff in the Departments of Radiology will evaluate the conventional studies. Dr. Chen reviews the F-DOPA PET/CT without knowledge of the results of other localization studies. Dr. Gharib reviews all studies. Data are maintained by the NICHD Clinical Trials DataBase.

The study will be analyzed in collaboration with Dr. Robert Wesley (Clinical Center Statistics Center). Data are collected and analyzed with regard to the sensitivity, specificity, accuracy, and predictive value for each scan being evaluated. The exploration and pathologic analysis is used as the reference standard. McNemar's test for evaluating paired data will be used (40). In addition to McNemar's test, other approaches to evaluation of the four objectives are below:

(a*) Compared to other imaging techniques, is the sensitivity and specificity of F-DOPA PET/CT higher in detecting the source of ectopic ACTH production in patients with known and unknown tumor localization?* To determine this, we will calculate the sensitivity, specificity, positive and negative values in patients with proven tumors and compare these with the results from the other modalities. Confidence intervals will be calculated and overlapping results will indicate that the modalities are similar. We cannot perform these calculations for unknown tumors, but can compare the overall percentage of tumors found of all imaged using each technique.

(b*) Does a correlation exist between F-DOPA uptake and the type of tumor, its size and proliferative activity?* To do this, we will evaluate the percent of each type of tumor that has a positive F-DOPA scan. Confidence intervals will be used to compare across tumor types. Univariate logistic regression will be performed using size and mitotic index as the variables.

(c) Can the administration of mifepristone, 600 mg daily for 10 days, convert a negative standard 6 mCi OCT (L-OCT) to a subsequent positive result? This will be a descriptive analysis, indicating the percentage of tumors that convert the test to a positive result. A post-hoc analysis will compare this percentage to the historical percentage of tumors that are positive on high but not low dose octreoscan.

(*d) Does gated chest MRI detect more lesions than routine MRI?* A similar approach will be used, to look at the percentage of known tumors that are detected by gated vs routine MRI and comparing confidence intervals around those values.

PHARMACEUTICAL AND RADIATION SAFETY

Pharmaceutical Information: F-DOPA

F-DOPA is a radiolabeled amino acid (^{18}F has a 109 minute half-time). It is approved by the FDA for use under IND # 35513. Dr. Peter Herscovitch, Chief, PET Department, holds the IND. F-DOPA is produced as outlined in the IND. F-DOPA has been used in many protocols at the NIH and at other centers throughout the world. The formulation is prepared on the day of use and assayed in a dose calibrator. The total amount of F-DOPA will typically be ~2.4 mg and will not exceed 6.5 mg.

Pharmaceutical Information: [^{111}In-DTPA-D-Phe]-pentetreotide

Pentetreotide is an analogue of octreotide (Sandostatin), produced by the addition of DTPA, which allows for the binding of metals such as Indium. Octreotide itself is an 8 amino acid cyclic peptide, biologically active analogue of the native somatostatin and has a longer plasma half-life than somatostatin. [^{111}In-DTPA-D-Phe]-pentetreotide is an FDA-approved agent that is obtained on a unit dose basis or prepared on-site in our radio pharmacy using commercial kits. Three 6 mCi standard low doses will be given for the high dose (~18 mCi) scan. Each 18 mCi high dose contains ~30 mcg Pentetreotide.

Radiation toxicity and adverse events

The research radiation doses that the patient will receive as a result of participating in this study are from the F-DOPA and its associated attenuation CT scan, and from the additional post-mifepristone L-OCT scan and attenuation CT scans used in conjunction with SPECT. The maximum possible radiation dose that patients will receive from these research studies is outlined in the 88-23a form.

F-DOPA

No toxicity has been associated with the administration of F-DOPA, although with increased use it is possible, although unlikely, that unanticipated side effects or allergic reactions may be observed from this DOPA analog. From 4/1/200 to 7/31/2004 128 F-DOPA scans were performed at the NIH using up to 17 mCi of F-DOPA. Any toxicity related to the F-DOPA-PET precludes repeat administration of the F-DOPA.

[^{111}In-DTPA-D-Phe]-pentetreotide (Octreoscan)

[^{111}In-DTPA-D-Phe]-pentetreotide is excreted almost exclusively by the kidneys, with hepatobiliary excretion accounting for approximately 2% of excretion. After injection, plasma clearance is rapid such that at 10 minutes, only approximately 33% of the injected dose remains in the blood pool. The physical life of [^{111}In-DTPA-D-Phe]-pentetreotide is approximately 2.8 days (67.3 hours). The biologic half-life of [^{111}In-DTPA-D-Phe]-pentetreotide is approximately 6 hours.

[^{111}In-DTPA-D-Phe]-pentetreotide has been shown in nonclinical pharmacological studies to have 1/10 the hormonal effect of octreotide in vitro when 3 or 6 mCi dose was used (package insert). Because of these decreased hormonal effects and the fact that the dose of pentetreotide administered during this study is approximately 10 or 30 mcg, which is 2.5-10 times less than the usual dose of octreotide prescribed for therapy, no hormonal effects are expected to result from the radiopharmaceutical administration. As stated in the package, in clinical trials of 538 patients, less than 1% experienced the following: dizziness, fever, hypotension, changes in liver enzymes, joint pain, nausea, sweating, and weakness. These were transient. To date, no patients at NIH have reported any adverse side effects after receiving [^{111}In-DTPA-D-Phe]-pentetreotide (> 600 doses administered).

Mifepristone (HRA 052015; INN Mifepristone)

Mifepristone is a cortisol and progesterone analog with antiglucocorticoid and antiprogestin activity. Healthy subjects receiving long-term mifepristone administration showed antiglucocorticoid effects at a daily dose of 10 mg/kg, which is about 5 – 10 fold greater than that required to demonstrate antiprogestin

effects (41). The agent can effectively reverse the clinical and glucocorticoid-dependent biochemical features of CS (42).

The dose (200 mg three times daily) is close to the median dose (732 mg daily) found effective in improving diabetes in patients with Cushing's syndrome (43). The duration of dosing is arbitrary. There are no data in animals regarding up-regulation of somatostatin receptors in vivo. However, receptors are restored in vitro within 24 hours (18). Because octreoscans must be given at least one week apart according to nuclear medicine a shorter dosing interval is not possible. We have elected to give the agent thrice daily to ensure constant levels. Previous pharmacokinetic studies used an older formulation of the agent; until new PK studies are done we think that this is a conservative approach. In patients who have UFC $\geq$ 10-fold normal we will double the dose for 24 hours before and continuing until the 24-hour scan.

Mifepristone will be given under an active IND (70,795) sponsored by Laboratoire HRA Pharma, NICHD's collaborative research and development agreement (CRADA) partner, which is investigating the utility of mifepristone for the treatment of ectopic ACTH secretion at the NIH and other sites. HRA Pharma will provide mifepristone in 200 mg tablets packaged as 50 tablets in 5 blister packs. Mifepristone will be manufactured, controlled and released according to current GMP guidelines.

Adverse events and monitoring plan

All adverse reactions occurring during the study, either observed by the physicians or nurses or reported by the patient, will be recorded.

Dr. Nieman is responsible for communication of events related to the IND. We will report to the Sponsor those adverse events occurring within 24 hours of administration of F-DOPA (ten half-lives rounded up to the nearest day), within 7 days if serious and 14 days if not serious. We will report similarly to Laboratoire HRA Pharma (mifepristone sponsor) any event occurring during or within 10 days after the last dose of mifepristone administration (about 24h half-life). Specifically, report will be by telephone to the NIDDK Clinical Director and NIDDK/NIAMS IRB and IND holders (Dr. Peter Herscovitch 301-451-4248 for F-DOPA, Dr. Erin Gainer, Laboratoire HRA Pharma for mifepristone).

Unanticipated problems will be reported to the IRB within 7 days if serious, and 14 days if not serious. Minor deviations in the conduct of standard medical care and imaging, such as missing timepoints on a test, or decisions not to schedule all possible imaging (for example, not scheduling pelvic imaging in a patient with a possible lung mass) will not be reported to the IRB or sponsor. All other anticipated or unanticipated adverse events related to the research studies will be reported in aggregate to the sponsor and IRB at the time of annual reports. Examples of expected adverse events include but are not limited to those events detailed in the Investigators' Brochure for mifepristone and in the protocol's risk section, as well as pulmonary embolism, other thromboembolic events, hypertension, worsening of pre-existing conditions, infection, and the like, which are common in patients with Cushing's syndrome. These would be reported to the IRB only if they become unanticipated problems.

In the unlikely event that any untoward or unexpected outcomes occur, the patients will be treated for all immediate medical problems (e.g. anaphylactic reaction) in an appropriate setting (e.g. ICU). Any patient withdrawn or discontinued from the present study is not reinstated. The occurrence of a serious adverse reaction will prompt review and there will be no further subject accrual until a thorough investigation into the cause has been completed and it is deemed safe to continue.

There is no DSMB associated with this study. We have revised the NICHD Clinical Protocol Monitoring Plan to add that HRA Pharma will monitor the study for the use of mifepristone; we continue to request NICHD monitoring of the F-DOPA portion of the study.

REGULATORY DOCUMENTATION

Source Documentation and Case Report Forms

The research staff documents data pertinent to eligibility and medical care during the admission. Research scans are reviewed at intervals with the study radiologist and recorded. Biochemical data are reviewed but not transcribed in toto from CRIS and eligibility is confirmed at a meeting of the research team.

IRB and DSMC Documentation

The Principal Investigator, Dr. Nieman, is responsible for maintaining IRB correspondence. Documents

The Principal Investigator, Dr. Nieman, is responsible for maintaining IRB correspondence. Documents retained in the files include each submission to each committee, the committees' findings, the investigators' responses and the final approval sheets.

FDA Documentation
Dr. Nieman is responsible for communications related to the IND. Dr. Herscowitz is the sponsor of the study. Annual reports are sent to him regarding study progress.

Adverse Event Procedures and Documentation
Events are reported as described above.

Study Completion
Per the CRADA agreement, those study files and data will be maintained indefinitely; however, this may change depending on the circumstances surrounding closure of the study.

HUMAN SUBJECTS PROTECTIONS

Rationale for Subjects Selection

Adults of any ethnic and racial group are invited to participate. Exclusion and inclusion criteria are listed above. Since radiation is used, no pregnant or lactating women are studied.

Advertisement, Recruitment, and Payment

The study is posted on the Clinical Center www protocol site, which explains the characteristics of the patients sought and the main purposes of the study. A phone number is listed, where inquirers can obtain more information and enter a mailing list for receiving information packets, including consent forms. Any other advertisement will be submitted to the IRB for approval.

NIH employees may participate in this protocol. Patients do not receive payments or compensation. Travel costs may be provided after the initial visit, or including the initial visit if there is financial need.

Benefits, Risks, and Hazards

Benefits

Patients benefit from initial and follow-up general and endocrinologic evaluations, including imaging studies. Patients in whom a tumor causing ectopic Cushing syndrome is found are offered surgery at the NIH. Those with Cushing's disease may undergo surgery at the NIH. Patients with hypercortisolemia due to occult tumor will be offered medical treatment (i.e. administration of drugs blocking cortisol synthesis or cortisol action) or bilateral adrenalectomy.

Since there is a possibility that patients may benefit from detection of previously unrecognized tumor, information gained from this study may affect future clinical management of patients with ectopic Cushing syndrome.

This is an elective study. Thus, nonparticipation does not affect a patient's clinical care, but patients electing not to participate in the research component will be returned to the care of their outside physicians.

Risks and Hazards

1. *Risks related to radiation* from the administration of radioactive drugs and attenuation CT scans. The annual total effective research radiation dose to patients receiving both FDOPA PET/CT and L-OCT after mifepristone, is 3.12 rem. It will be correspondingly less for those who receive only one of these research studies. (Please also see Concern About Radiation" above re: radiation from other studies). To minimize bladder exposure, FDOPA patients will be asked to void after approximately 30 min., and every 90 minutes for the 6 hours following completion of the PET scan. Patients will be asked to void every 2 – 4 hours for 12 hours after the Octreoscans.

2. *Vein cannulation* can cause pain, bleeding, thrombosis, or infection. Bleeding is prevented by local pressure applied for 5-10 minutes after catheter removal. Infection is prevented by use of clean technique and the relatively short time the catheter is in place. Fainting can occur during insertion of a vascular catheter in subjects who are sitting; however, in this study, the subjects are supine. An indwelling line will be placed to reduce the number of needle sticks needed for phlebotomy purposes.

3. *Vein cannulation for IPSS* may cause femoral hematoma, arteriovenous fistula, bruising or discomfort or transient arm anesthesia. Femoral vein puncture is sometimes more difficult in patients with Cushing syndrome because of marked obesity. There is a slight, but definite risk of entering the femoral artery that might result in bleeding, a groin hematoma or arteriovenous fistula. However, we currently have available a "smart" needle with an ultrasound transducer incorporated in the tip which enables us to puncture veins even in the most difficult subjects so that we anticipate < 1% rate of these complications. Patients experience mild discomfort and may have visible bruising in the groins after the procedure. Cannulation of the internal jugular vein led to transient loss of sensation in the arm in one patient at the NIH, presumably because of infiltration of the cervical nerves by the anesthetic.

4. *CRH administration* has minimal risk. Up to 20% of patients experience flushing and a smaller percentage experience a metallic taste. CRH has been given safely on multiple occasions to the same patients, as proposed here, in the context of CRH stimulation test or dexamethasone test. CRH has been given more than 1000 times at the NIH and many thousands of times world-wide. The commercially available formulation is used (Ferring Corp.).

5. *Contrast allergy* to radiographic dye. There is a very small (< 0.5 %) risk of new contrast allergy. Patients with a known dye allergy will receive prophylactic treatment.

6. *Anemia*. The maximum total amount of blood drawn for the standard medical tests is about 265 ml. The study is not to be performed if the patient's previous and predicted total blood withdrawal for the six weeks prior to the study is more than 450 ml.

7. *The use of Foley or condom catheters*, if needed, may be associated with some local discomfort and an increased risk of urinary tract infection.

8. *Possible emotional responses during scans*. A patient can develop nervousness, anxiety, and panic attacks during any scanning procedure. In such a case, the study is discontinued and the patient evaluated and treated if necessary.

9. *MRI evaluations may cause claustrophobia*. Should this occur the study will be stopped and re-scheduled with administration of a sedative.

10. *Risk of adrenal insufficiency due to mifepristone*. Subjects without Cushing syndrome who received long-term mifepristone administration showed antiglucocorticoid effects at a daily dose of 10 mg/kg, which is about 5 – 10 fold greater than that required to demonstrate antiprogestin effects (41). Overtreatment with mifepristone may lead to adrenal insufficiency. In case of suspicion of adrenal insufficiency (defined as hypotension and the presence of severe symptoms of nausea, vomiting or diarrhea), we will stop mifepristone and initiate glucocorticoid substitution with hydrocortisone or dexamethasone. Therapy will take into account results from pharmacology studies demonstrating that 1 mg dexamethasone or 30 mg hydrocortisone antagonizes 400 mg mifepristone. These individuals will not receive the second L-OCT.

Patients with isolated symptoms (nausea, vomiting, diarrhea, weight loss, anorexia or isolated fatigue) will be monitored closely as an inpatient in the Clinical Center. Except for diarrhea, these symptoms are expected possible effects of the study treatment and are not systematically indicative of adrenal insufficiency. No modification of treatment will be initiated unless symptoms worsen or patient develops new symptoms. Hyponatremia and/or hyperkalemia can be indicative of adrenal insufficiency but also can be explained by other causes and will require further investigation.

Less specific adverse events as maculopapular rash also have been observed.

11. Risks associated with use of gadolinium-based contrast agents(GBCAs) for magnetic resonance imaging(MRI). The FDA has issued a warning that certain groups of patients are at risk for nephrogenic

systemic fibrosis after receiving gadolinium. In order to reduce unnecessary risks, serum creatinine and GFR will be obtained prior to any gadolinium-based procedure. Gadolinium will be withheld in patients with acute or chronic renal insufficiency (GFR<60ml/min), unless deemed necessary in order to verify CT scan findings required for clinical management decisions. The vast majority of patients receiving gadolinium-based contrast agents have no symptoms related to the injection of this medication. Mild symptoms that may occur include coldness in the arm at the time of injection, a metallic taste, headache, and nausea. In an extremely small number of patients, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure

Consent Process and Documents

When patients or physicians contact the research team to indicate an interest in participating in the study, a consent form will be provided and any questions will be answered. The study will be explained verbally and all questions and concerns addressed at the first NIH visit, at which time written informed consent will be obtained. Members of the research team authorized to obtain consent are Dr. Nieman and Ms. Raven McGlotten. A record of communication of this information and of the consent to participate in the study is placed in the medical record and the patient receives a copy of the document. The research team retains a copy. The right of the subjects to withdraw from this study or to refuse any procedure is made clear.

Three consent forms will be used to reflect the various options available to current patients (based on number of previous scans) and for new patients. All returning patients will be consented again with the appropriate consent. These will include:
1. Consent for previous patients who have had their maximum of two F-DOPA PET examinations and three H-OCT examinations. On each admission they will get only standard clinical imaging (CT, MRI, 6 mCi OCT).
2. Consent for (previous or new) patients who are hypercortisolemic. On each admission they will get standard clinical imaging (CT, MRI, 6 mCi L-OCT) as well as F-DOPA PET/CT and one octreoscans with mifepristone. Because most patients are hypercortisolemic at only one visit, we anticipate that they would need a separate subsequent consent, unless they have recurrent disease.
3. Consent for (previous or new) patients who are hypercortisolemic and refuse or are not candidates for mifepristone, or those who are not hypercortisolemic. On each admission they will get standard imaging (CT, MRI, 6 mCi OCT) as well as F-DOPA PET and high dose octreoscan (if low dose is negative), up to the maximum number of PET and high dose octreoscans.
We do not plan or anticipate the enrollment of non-English speaking subjects; however they are not excluded from participation either. Should a non-English speaking subject be eligible for enrollment, IRB approval will be obtained for use of the short form consent process in the absence of a fully translated consent document as outlined in SOP 12.9.1, under the provisions of 45 CFR 46.117(b)(2). IRB approval will be obtained according to IRB guidance prior to obtaining informed consent from the potential study participant/s.

Employee enrollment is not anticipated in this protocol, but if an employee wants to be enrolled in the study with the prospect of direct benefit in accordance with the policy SOP 14F.3.1 the PI is not required to amend the protocol. However the PI will take the following steps to ensure that there are adequate protections in place to protect the confidentiality of employee health information and minimize any pressure or discomfort of the employee with consent process.

1. The PI or responsible AI will make the NIH Information Sheet on Employee Research Participation available to employees who are considering enrolling in research to help them understand the possible consequences. Also, the PI or AI will make a copy of the NIH policy 2300-630-3 available to employee.
2. If PI or AI is the supervisor of the employee-subject an independent person (i.e. bioethics staff) will monitor consent process.
3. The PI will require that study staff who may have contact with sensitive data about a co-worker or subordinate complete the Just-in-Take CITI course “Biomedical –Vulnerable Subjects-Workers/Employees”.

Confidentiality and use of retained tissue specimens

Confidentiality of patients is assured according to the laws of the State of Maryland. When results of a study such as this are reported at meetings or in medical journals, the identification of those patients taking part is withheld. Medical records of Clinical Center patients are maintained according to current legal requirements and are made available for review, as required by the FDA or other authorized users

legal requirements and are made available for review, as required by the FDA or other authorized users, only under the guidelines established by the Federal Privacy Act. All data are kept in locked files.

Patients will be asked to consent to the future use of urine, blood and tumor samples. If they consent to such use, samples may be used in the future, with identifiers, for studies not described here, without obtaining new informed consent. Only studies related to Cushing's syndrome or the biology of tumors would be undertaken. Investigators who are not part of this protocol may procure tumor tissue in the operating room only with authorization from Dr. Nieman. Tissue samples may be shared with collaborators, without personal identifiers. All samples will be coded without personal identifiers and will be stored in accordance with NIH and NICHD biospecimen policies.

Other Interested Parties and Collaborators

The NIH has a Cooperative Research And Development Agreement (CRADA) with Laboratoire HRA-Pharma, in Paris, France. The intention of the CRADA is to develop mifepristone for the treatment of Cushing's syndrome, for use as an adjunctive agent for Octreoscan, and for use as a diagnostic agent.

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