PET PROBE FOR THE DOPAMINE TRANSPORTER: [^{18}F]FECNT

A. INVESTIGATOR: Robert Innis, MD, PHD, MIB NIMH

B. RADIOTRACER:

[^{18}F]2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-^{18}F-fluoroethyl)nortropane ([^{18}F]FECNT), which binds reversibly to the dopamine transporter (DAT), will be prepared by the NIMH PET Radiochemistry Laboratory, under the supervision of Dr. Victor Pike.

C. HUMAN RADIATION DOSIMETRY ESTIMATES FOR [^{18}F]FECNT:

Dr. Goodman's group at Emory University has preformed human dosimetry estimates (Deterding et al 2001). These estimates were derived by extrapolation to humans of rat and monkey biodistribution data using the MIRD approach. Deterding et al. (2001) did not obtain urine activity measurements and did not apply a dynamic bladder model. For these reasons, the NIH Radiation Safety Committee asked that we confirm these data in whole body imaging in three monkeys. This study has been completed, and our report is attached.

D. HUMAN SAFETY DATA:

As of March 20, 2003, Emory University has studied 35 individuals, with [^{18}F]FECNT. The majority were healthy subjects and a minority had Parkinson's disease. NIMH paid Emory University to obtain safety data on 10 healthy subjects. The mean injected activity ± SD was 6.3 ± 2.0 mCi, with a specific activity of 0.2 ± 0.2 Ci/μmol, and mass of 21 ± 24 μg. The range of mass doses was 2.3 - 86 μg.

We request permission to inject a maximum of 3 μg, which is among the lowest doses studied at Emory. For an injected dose of 10 mCi, the specific activity would be 1.1 Ci/μmol.

The mass dose of [^{18}F]FECNT requested in this application is calculated to occupy less than 1% of dopamine transporters in striatum (see below). Thus, [^{18}F]FECNT is being used at tracer doses, and no pharmacological effects would be expected. By contract with NIMH, Emory University carefully monitored nine representative subjects with vital signs, EKG, blood and urine tests before and after injection of the radiotracer. Details of this monitoring study are provided below. In brief and as expected, the tracer doses of [^{18}F]FECNT used for PET imaging showed no pharmacological effects. To further confirm this lack of pharmacological effect, we will obtain tests of safety in the initial group of subjects undergoing whole body imaging. Specifically, we will record vital signs (ECG, heart rate, blood pressure, and respiration rate) before, ~15 min after, and 30 - 60 min after tracer injection. The measurement before tracer administration will be done within 3 h before tracer administration. In addition, approximately 24 h after tracer administration, the screening LABORATORY TESTS described in the IRB protocol will be repeated.

Dr. Mark Goodman at Emory University performed safety monitoring studies on contract to NIMH. Ten healthy humans were studied: 4 males and 6 females, 29 ± 8 y. These subjects all had negative drug screening prior to

participation. As described below, injection of [^{18}F]FECNT caused no detectable pharmacological effects.

1. Vital Signs

Heart rate and blood pressure were measured five times (one before administration and four times after injection). There was no clinically significant change in vital signs.

2. Subjective and Objective Assessment of Psychiatric and Neurological Effects.

No subject reported any psychiatric or neurological symptoms nor were there any signs related to [^{18}F]FECNT administration.

3. Electrocardiograms

ECG was recorded before tracer administration, and within 15 min and between 30 and 60 min after tracer administration. No subject showed abnormal ECG after tracer administration.

4. Laboratory Tests

Laboratory tests consisted of glucose random, sodium, potassium chloride, CO_2, urea, creatinine, ALT, AST, protein, albumin, alkaline phosphatase, bilirubin, calcium, phosphorus, uric acid and creatine kinase as well as CBC with differential counts. These tests were performed at baseline and 1 d after tracer administration. No subject showed any clinically significant changes in the lab tests after tracer administration.

E. PHARMACOLOGICAL EFFECTS OF NON-TRACER DOSES OF FECNT:

As would be expected for a tracer dose, [^{18}F]FECNT has been administered to human subjects with no detectable pharmacological effects. [^{18}F]FECNT is a substituted tropane and structurally similar to many other DAT imaging agents that have been used in human subjects. As a dopamine transporter blocking agent, if it were given in pharmacological doses, one would expect increased heart rate and blood pressure, elevated mood, and hyperactivity. Imaging agents very similar to [^{18}F]FECNT have been studied in thousands of subjects and several patient populations, including Parkinson's disease, depression, and cocaine addiction. Dr. Innis studied more than 1,000 subjects at Yale with the closely related iodinated analog [^{123}I]β-CIT (2β-carbomethoxy-3β-(4-iodophenyl)tropane). There were never any adverse reactions, nor any detectable pharmacological effects. In fact, another analog of [^{18}F]FECNT has been commercialized and is available in Europe to aid in the diagnosis of Parkinson's disease: [^{123}I]FPCIT under the name Datscan®.

Estimation of % occupancy of DAT binding sites by 3 μg injection of [^{18}F]FECNT

Percent occupancy of DAT binding sites was calculated based on the brain uptake of [^{18}F]FECNT and DAT density measured in postmorten human brain. The data from Dr. Goodman suggest that the concentration of [^{18}F]FECNT in striatum from a 10 mCi dose with specific activity of 1.1 Ci/μmol (i.e., mass dose of 3 μg) is ~0.8 nM in striatum, the region of brain with highest uptake. Postmortem studies have shown that the density of DAT in human striatum is ~140 nM (Little et al 1995). If all the activity in striatum were bound to the transporter (which is an overestimation), then the occupancy would be 0.8 / 140 = 0.6%.

References

Deterding TA, Votaw JR, Wang CK, et al (2001): Biodistribution and radiation dosimetry of the dopamine transporter ligand. *J Nucl Med* 42:376-81.

Little KY, Carroll FI, Cassin BJ (1995): Characterization and localization of [125I]RTI-121 binding sites in human striatum and medial temporal lobe. *J Pharmacol Exp Ther* 274:1473-83.