Assessment of 21-[^{18}F]Fluoro-16α-Ethyl-19-Norprogesterone as a Positron-Emitting Radiopharmaceutical for the Detection of Progestin Receptors in Human Breast Carcinomas

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We have used 21-[^{18}F]fluoro-16α-ethyl-19-norprogesterone (FENP) for imaging progestin receptors by PET in patients with primary carcinoma of the breast. In vitro binding and in vivo tissue distribution studies in rats have shown that FENP has high specific activity, high affinity for progestin receptors, and receptor-mediated uptake in target tissues. Eight patients with primary breast carcinoma were studied. Breast carcinoma was identified correctly in 50% of the patients with progestin-receptor-positive tumors; however, the FENP uptake was not correlated with progestin-receptor levels. We noted a low target-to-background ratio in humans, with high relative activity in the spine, blood pool, and normal breast tissue. Our findings indicate that FENP is not a suitable agent for imaging progestin receptors in humans.

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Steroid receptor-based imaging agents for use in studying breast cancer have been developed by several groups of investigators over the last decade. The emphasis of this research has focused mainly on estrogen receptors (*1–8*). We have used 16α-[^{18}F]fluoroestradiol-17β (FES) for imaging primary and metastatic breast cancers in humans by positron emission tomography (PET). In an initial study, we found an excellent correlation between the tumoral uptake of FES on the PET images and the tumor estrogen-receptor concentration measured in vitro (*9*). We subsequently have shown that PET with FES has potential for evaluating patients with metastatic breast carcinoma and for monitoring the effect of anti-estrogen therapy (*10*).

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It is well known that estrogen- and progestin-receptor levels in breast cancer are important predictors of tumor responsiveness to hormonal therapy (*11–13*). Horwitz and McGuire have hypothesized that endocrine-resistant estrogen-receptor-positive tumors have a defect in their response system (*14,15*), resulting in decreased progestin-receptor concentrations (since progestin-receptor synthesis is estrogen controlled). Therefore, the presence of progestin receptors may signify a functionally intact estrogen-response mechanism, and imaging based on the progestin receptor rather than the estrogen receptor might serve as a better predictor of endocrine responsiveness. Indeed, progestin-receptor positivity has shown a stronger correlation with the response to hormonal therapy in clinical studies than has estrogen-receptor positivity (*16,17*). Furthermore, in patients receiving hormonal therapy (e.g., tamoxifen) for estrogen-receptor-positive tumors, the tumor estrogen receptors would be occupied by tamoxifen and its metabolites, compromising PET imaging with positron-emitting estrogen-receptor ligands (*10*). In contrast, the progestin receptors of such patients should remain unoccupied, and the progestin-receptors level of their tumors may even be elevated (*18,19*). Additionally, progesterone imaging agents might be of use in estrogen-receptor-negative, progestin-receptor-positive patients, a group that comprises 5%-10% of patients with breast cancer (*20*).

We have recently synthesized and characterized the radiofluorinated steroid compound, 21-[^{18}F]fluoro-16α-ethyl-19-norprogesterone (FENP), an analog of the potent progestin ORG 2058, in which the 21-hydroxyl group is replaced by a fluorine atom (*21*). FENP is itself a potent progestin, possessing a high binding affinity (60 times that of progesterone) for the progestin receptor (*21,22*). FENP is easily synthesized with yields of 10%-20% and with high specific activity in a two-step procedure from ORG 2058

(*21*). Biodistribution studies with FENP in estrogen-primed rats treated with tamoxifen showed highly selective uterine uptake and excellent uterus-to-blood and uterus-to-muscle ratios (*21*). Because of the favorable characteristics of FENP, we hypothesized that it should be an excellent radiopharmaceutical for human breast cancer imaging. Consequently, we undertook this study to evaluate FENP for imaging of progestin receptors by PET in primary breast carcinoma.

METHODS

This investigation was approved by the Human Studies Committee and the Radioactive Drug Research Committee of the Washington University School of Medicine. Eight adult nonpregnant women (mean age 53.4 yr; range 39–72 yr), who had mammographic findings highly suspicious for primary breast carcinoma and who were scheduled for biopsy, participated in the study. Informed consent was obtained from each patient. In vitro assays for progesterone and estrogen receptors were performed on the biopsied material from all patients.

FENP was prepared by a robotic adaptation of the synthesis reported by Pomper et al. (*21*). The effective specific activity of FENP (generally 700–1400 Ci/mmol of receptor-binding mass) was assessed on decayed samples of known initial radioactivity by competitive binding assay (*21,23*, and Katzenellenbogen JA et al., unpublished observations).

Each patient received approximately 5 mCi of FENP by intravenous injection. The whole-body radiation exposure from 5 mCi of FENP was estimated to be 243 mrem and that to the lower large intestine (the tissue receiving the highest exposure) was 4600 mrem, based on biodistribution studies in rats (unpublished data). Imaging was performed on Super PETT IIB, a time-of-flight positron tomograph with an intrinsic spatial resolution of 4.5 mm in the transaxial dimension. Seven simultaneous sections were obtained over an axial field of view of 9.8 cm. The scanner was operated in the low-resolution mode, yielding a slice thickness (full width at half maximum) of approximately 11 mm; image reconstruction filters were selected to provide a transaxial resolution of approximately 10 mm (full width at half maximum). Each patient was positioned supine in the scanner so that the detector array was at the level of the breast mass (as determined by mammography and physical examination). A 20-min emission scan was then performed, beginning approximately 90 min after injection of the radiopharmaceutical. In two subjects (Patients 4 and 5), imaging was performed continuously during the period from 0 to 110 min postinjection, and serial 10-min reconstructions were generated for dynamic time-activity-curve analysis. Immediately after emission imaging, all patients underwent a 15-min transmission scan performed with a rotating $^{68}Ge/^{68}Ga$ sector source. Appropriate attenuation images were reconstructed and backprojection attenuation files were utilized for emission image reconstruction. The images were reviewed independently by two nuclear medicine physicians (AHM and BAS) experienced in interpretation of PET images. These observers, who were blinded with respect to clinical and radiographic findings, determined the presence or absence of focally increased uptake of the radioligand in the breasts. The two observers agreed in all instances. The interpretations of the images were then correlated with the radiographic and surgical findings.

Regions of interest (5 × 5 pixel, 2.9 cm^2) were placed over the area of peak activity in the breast mass, over a symmetrically positioned site in the contralateral breast (for estimation of nonspecific uptake in breast tissue), and over the heart (for estimation of blood-pool activity), the spine, and the liver (in three subjects whose livers were in the field of the view of the PET scanner). The mean regional activity (±s.d.), measured on PET images, was calculated for each region of interest and expressed as the percentage of the injected dose per milliliter (%ID/ml).

RESULTS

Pertinent data for the eight patients who participated in the study are shown in Table 1. Selected PET images are shown in Figure 1. The breast masses ranged from 1.5 to 9 cm in maximum diameter. The breast mass of Patient 6 was not included in the field of view of the PET scanner due to an error in positioning; therefore, her study could not be evaluated further. The activity level in each breast mass was compared to that of the corresponding site in the contralateral breast. Uptake in the breast mass was increased relative to normal breast tissue in Patients 2, 4,

TABLE 1
Summary of Clinical, Imaging, and Receptor Findings

Patient no.	Age (yr)	Maximum tumor diameter (cm)	PET results	Receptor Concentration (fmol/mg protein)		FENP specific activity (Ci/mmol)
				Estrogen	Progestin	
1	58	1.5	–	60	20	10,853
2	39	2.0	†	93	152	10,853
3*	47	4.0	–	<3	80	8,162
4	45	9.0	†	53	15	516
5	47	3.0	–	32	222	3,836
6	72	2.5	NIF	108	64	1,990
7	61	5.0	†	72	150	3,596
8	58	6.0	–	58	<5	3,583

* The receptor levels were measured following chemotherapy.
† Increased FENP uptake in breast mass.
– No increased FENP uptake in breast mass.
NIF = tumor not in the field of view of PET scanner.

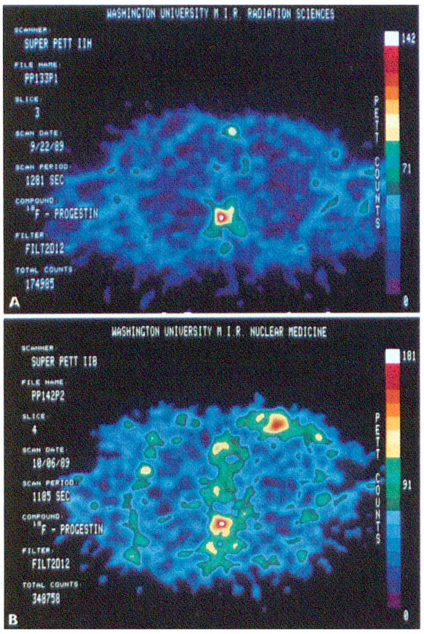

FIGURE 1. Representative transaxial PET images with FENP at the level of the primary breast carcinoma. (A) The image of Patient 3 shows no increased activity in the region of the right breast mass (although the greater size of this breast is apparent). Vertebral and sternal uptake, presumably of free [^{18}F]fluoride, are noted. (B) The image of Patient 4 shows focally increased activity in the left breast mass, as well as increased activity in a thoracic vertebra, several ribs, and the mediastinal great vessels.

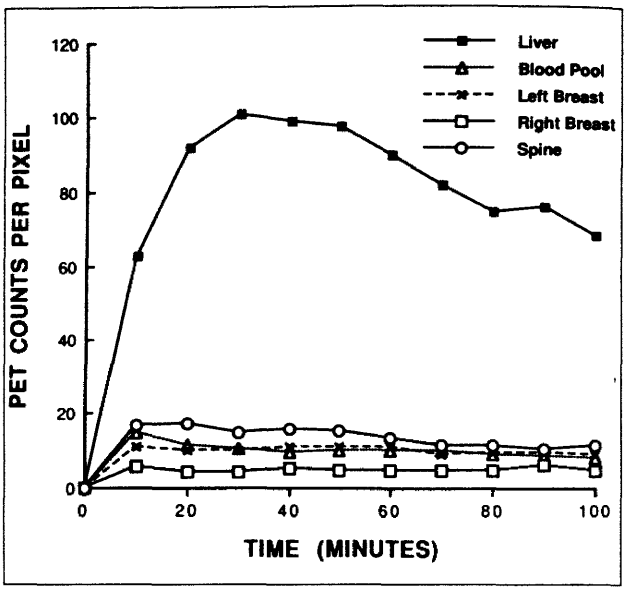

FIGURE 2. Time-activity curves generated from the continuous data collection from 0 to 100 min after injection of FENP in Patient 4. Greatest activity (expressed in PET counts per pixel) is apparent in the liver, with peak uptake noted at about 30 min. The uptake in the tumor (left breast) is about twice that in the normal right breast, but is less than that in the spine and about equal to blood-pool activity. These findings correspond well with the appearance of this patient's image shown in Figure 1B.

and 7, while no tumor-specific uptake was seen in the remaining four patients (Table 1). The tumor estrogen- and progestin-receptor levels were positive in all patients except for Patient 8, whose tumor proved to be progestin-receptor negative, and Patient 3, whose PET study was performed prior to chemotherapy [Lippman's protocol (*24*)], but whose tumor receptor levels were measured following the chemotherapy and found to be estrogen-receptor negative and progestin-receptor positive at that time. The effective specific activity of the FENP injectates ranged from 516 to 10853 Ci/mmol, and was greater than 1900 Ci/mmol in seven of eight instances (Table 1).

Time-activity curves for the tumor, contralateral breast, spine, blood pool, and liver for the two patients who underwent dynamic studies (Patients 4 and 5) are shown in Figures 2 and 3, respectively. Prominent hepatic uptake was noted in the scan of Patient 4. Vertebral and blood-pool activity were higher than that of the breast tumors in both patients. A comparison of the hepatic activity levels (corrected for the injected doses of the radiopharmaceuticals) in one subject who received FENP and in another subject from our previous study with FES (10) is shown in Figure 4. The peak hepatic activity level for FENP was approximately 2.5 times greater than that for FES.

The images of the seven patients, whose breast masses were in the field of view of the PET scanner, were quantitatively evaluated. The mean [±s.d.] tissue activity (expressed as %ID/ml) was 1.31 [±0.79] $\times 10^{-3}$ for tumor, 1.02 [±0.39] $\times 10^{-3}$ for contralateral breast, 1.43 [±0.67] $\times 10^{-3}$ for blood pool, and 2.32 [±0.86] $\times 10^{-3}$ for spine. The liver activity was evaluated in two of the seven patients and the subject where the tumor was not in the field of

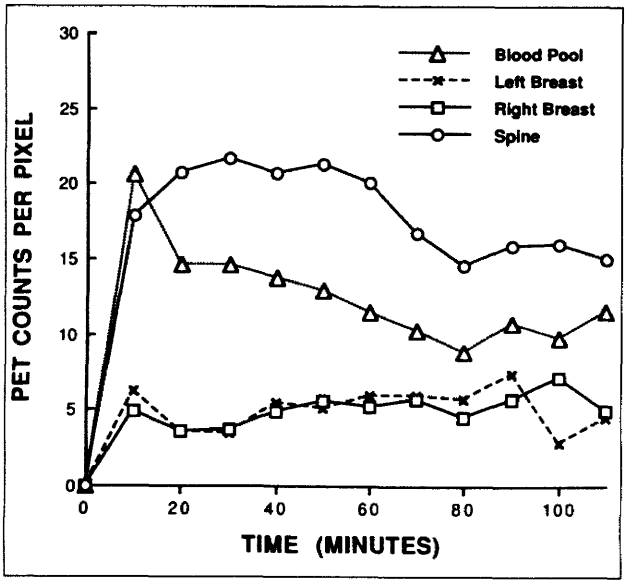

FIGURE 3. Time-activity curves generated from the continuous data collection from 0 to 110 min after injection of FENP in Patient 5. The activity (expressed in PET counts per pixel) of the tumor in the left breast is nearly identical to that of the normal right breast and less than that of the blood pool and spine.

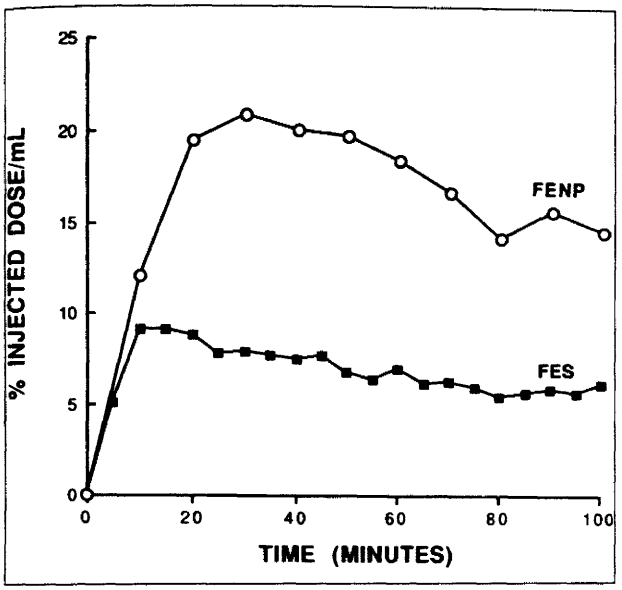

FIGURE 4. Hepatic time-activity curves generated from continuous data collections in two different patients from 0 to 100 min after injection of FENP and FES, respectively. The hepatic uptake (%ID/ml) of FENP is nearly twice that of FES.

view. Liver activity was 14.0 [±2.1] × 10^{-3} %ID/ml. There was relatively high nonspecific uptake of FENP in normal breast tissue, with no statistically significant difference between tumor activity and that of contralateral breast tissue ($p > 0.10$).

DISCUSSION

Despite the high affinity that FENP has shown for progestin receptors and its selective uptake in target tissues in rats (*21*), only 50% of progestin-receptor-positive primary breast tumors (3 of 6) were identified by PET with this radioligand in humans. Moreover, it appears that the uptake of the tracer was not correlated with the tumor progestin-receptor concentration.

Successful imaging of steroid-receptor-positive tumors requires radiotracers that have: (a) appropriately high-specific activity (because the receptors are saturable systems with limited uptake capacity), (b) high affinity for the desired receptor target coupled with (c) low non-receptor binding and, finally, (d) appropriate metabolism and clearance characteristics (*25*). FENP appears to fulfill the first two of these characteristics adequately. A theoretical calculation of the lower limit of specific activity required for steroid-receptor imaging, based on assumptions of the uptake level necessary for tumor detection, the receptor concentration and fractional receptor occupancy, suggests that a specific activity greater than 1000 Ci/mmol is necessary for adequate human tumor imaging with PET (*25*). With the exception of that used in Patient 4, all doses of FENP injected were well above this theoretical lower limit. Patient 4 (Fig. 1) had the highest FENP uptake in the breast tumor relative to that in the contralateral breast among our patients, despite having a relatively low progestin-receptor concentration and an FENP preparation with low specific activity (Table 1). Patient 5 had a negative image, while the progestin-receptor concentration of her breast tumor was the highest among all seven patients and the specific activity of the FENP administered to her was close to 4000 Ci/mmol. These results are unexplainable in terms of the simple theoretical concepts of radiotracer binding by receptors. Presumably, some factor other than specific activity is limiting the uptake of FENP by tumors.

With regard to the second characteristic, high affinity for the progestin receptor, FENP also appears adequate. The affinity of the progestin receptor for its natural ligand, progesterone, is lower (about 5 n*M*) than is the affinity of binding of other sex steroids (androgens and estrogens) to their cognate receptors (about 0.3 n*M*) (*26*); in fact, the affinity of progesterone is not sufficient to achieve receptor-mediated localization in target tissues in the rat (*27*), whereas higher-affinity synthetic ligands for the progestin receptor (e.g., ORG 2058 and R5020) do show selective uptake. FENP binds to rat progestin receptor with an affinity 60 times that of progesterone and several-fold greater than that of ORG 2058 and R5020. Although the rat and human progestin receptor have somewhat different binding specificity (*22*), FENP affinity in these two species is comparable (Carlson KE, unpublished observations). Thus, the affinity of FENP for the progestin receptor appears to be adequate.

With regard to non-receptor binding, metabolism and clearance, FENP is a less ideal tracer, since it is a relatively lipophilic compound, with a moderate level of nonspecific binding. Accumulation of the tracer in adipose tissue was noted in the preliminary studies in rats (*21*), and this could account, in part, for the high level of nonspecific uptake in normal breast tissue.

It is instructive to compare FENP, a progestin-receptor-based agent that shows selective uptake in rats (*21,28*) but not in humans, with FES, an estrogen-receptor-based agent that shows good uptake in target tissues in animals (*7*), but has also proved useful for imaging estrogen-receptor-positive tumors in humans (*9,10*). Very similar target-to non-target ratios were obtained for FES and FENP in the animal models, and the measured estrogen-receptor concentration in the immature rat uterus and the progestin-receptor concentration in the estrogen-primed rat uterus are comparable (within 15%) (*29*). One major difference, however, in the biodistribution of the two compounds appears to arise from differences in their clearance, namely, the greater hepatic uptake of FENP, which in the rat 1 hr after administration of the tracer is 2.7 times greater than the hepatic uptake of FES. Our limited comparison of the hepatic clearance of FENP and FES in patients (Fig. 4) shows that there is rapid uptake of both compounds by the liver; however, the peak uptake was 2.5 times greater with FENP.

Analysis of metabolic products of both FENP and FES in the blood of intact rats and in isolated rat hepatocytes (*30*) showed different metabolic profiles. Only very hydrophilic metabolites were observed with FES, while a significant fraction of the metabolites of FENP were hydrophobic. In vivo, hydrophobic metabolites will be taken up by muscle and fat to a much greater extent than hydrophilic metabolites. The greater hepatic uptake of FENP is likely to lead to a greater contribution to peripheral activity from such hydrophobic metabolites. Additionally, it is possible that there are differences in the metabolism of FENP in rats and humans, such that greater production of hydrophobic metabolites in humans makes FENP ineffective as a progestin-receptor imaging agent. Metabolic differences between rats and humans have been observed with many compounds (*31*).

We also noted slightly greater activity in the spine and blood pool relative to that of the breast lesions. The elevated osseous activity is most likely caused by metabolic defluorination of FENP with resultant accumulation of [^{18}F]fluoride in bone. This finding in humans also is consistent with the observation of high osseous uptake of this tracer in rats (*21*).

Thus, although the specific activity and receptor-binding affinity of FENP are adequately high, it appears that its moderate nonspecific binding and, particularly, what appear to be differences in the clearance and metabolism of this compound in the human versus the rat make it unsuitable as a progestin-receptor-based imaging agent in humans.

Considering the importance of progestin-receptor status in evaluating endocrine responsiveness of breast carcinoma, the need for a progestin-receptor-based imaging agent is obvious, and further effort should be made to develop such an agent.

ACKNOWLEDGMENTS

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SELF-STUDY TEST

Gastrointestinal Nuclear Medicine

Questions are taken from the *Nuclear Medicine Self-Study Program I*, published by The Society of Nuclear Medicine

DIRECTIONS

The following items consist of a heading followed by numbered options related to that heading. Select those options you think are true and those that you think are false. Answers may be found on page 1616.

Methods suitable for preparing a radiolabeled solid meal that is stable in gastric contents include which of the following?

19. Inject a live chicken intravenously with ^{99m}Tc-sulfur colloid. Kill the chicken 30 min later and remove the liver. Cook the liver by boiling it in water for 20 min.
20. ^{111}In-DTPA mixed with beef stew.
21. ^{99m}Tc-sulfur colloid mixed with a beaten raw egg and cooked until firm.
22. ^{99m}Tc-sulfur colloid mixed with canned liver pate, then fried and blotted on paper towels.
23. ^{51}Cr-sodium chromate mixed with a beaten raw egg and cooked until firm.
24. ^{131}I-labeled α-cellulose mixed with cheese spread.
25. [^{99m}Tc]pertechnetate mixed with liquid pancake mix, egg, and flour, and cooked on a griddle until done.

A 38-yr-old man with insulin-dependent diabetes mellitus is referred for a gastric empyting study. At the time of the initial study (Figs. 19A-B), the patient has mild symptoms characterized by occasional nausea and vague upper abdominal fullness. After the initial study, the patient was placed on oral metoclopramide and a follow-up gastric emptying study (Figs. 20A-B) was performed. The $T_{½}$ values for the gastric emptying studies are summarized in Table 1.

True statements concerning the results of both of these studies include which of the following?

26. Because the $T_{½}$ values for gastric emptying of both solids and liquids are normal, the patient's symptoms are not attributable to gastroparesis.
27. To reduce the radiation burden to the subject, one could eliminate studying the liquid phase of gastric emptying without losing clinically relevant information.
28. Treatment with metoclopramide has had no significant effect on the gastric emptying of solids.
29. Any improvement in the patient's symptoms with metoclopramide was likely due to both a direct increase in gastric motility as well as central nervous system effects.

(continued on p. 1604)

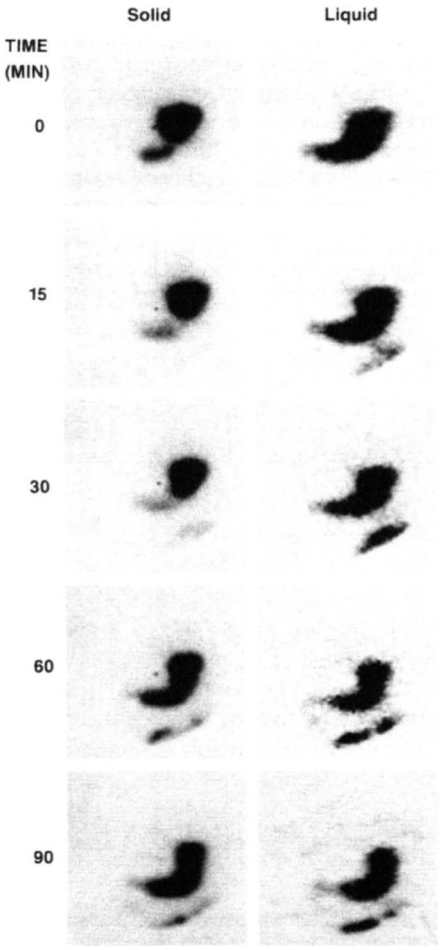

Figure 19A