6-[\textsuperscript{18}F]Fluorodopamine Positron Emission Tomographic (PET) Scanning for Diagnostic Localization of Pheochromocytoma

Karel Pacak, Graeme Eisenhofer, Jorge A. Carrasquillo, Clara C. Chen, Sheng-Ting Li, David S. Goldstein

Abstract—The diagnosis and treatment of pheochromocytoma depend critically on effective means to localize the tumor. Computed tomography and magnetic resonance imaging have good sensitivity but poor specificity for detecting pheochromocytoma, and nuclear imaging approaches such as \textsuperscript{131}I-metaiodobenzylguanidine scintigraphy have limited sensitivity. Here we report initial results using 6-[\textsuperscript{18}F]fluorodopamine positron emission tomography (PET) scanning in the diagnostic localization of pheochromocytoma. Twenty-eight patients with known or clinically suspected pheochromocytoma underwent PET scanning after intravenous injection of 6-[\textsuperscript{18}F]fluorodopamine. Of the 28 patients, 9 had surgical confirmation of the tumor, 8 had previously diagnosed metastatic pheochromocytoma, and 11 had plasma levels of metanephrines that were within normal limits. All 9 patients with surgically proven pheochromocytoma had abnormal 6-[\textsuperscript{18}F]fluorodopamine PET scans that identified the tumors. All 8 patients with metastatic pheochromocytoma had extra-adrenal sites of 6-[\textsuperscript{18}F]fluorodopamine-derived activity. Of the 11 patients with normal plasma levels of metanephrines, 9 had negative 6-[\textsuperscript{18}F]fluorodopamine PET scans, 1 had extra-adrenal foci of 6-[\textsuperscript{18}F]fluorodopamine-derived activity, and 1 had symmetric uptake of 6-[\textsuperscript{18}F]fluorodopamine in the region of the adrenal glands. In patients with known disease, 6-[\textsuperscript{18}F]fluorodopamine PET scanning can detect and localize pheochromocytomas with high sensitivity. In patients in whom the diagnosis of pheochromocytoma is considered but excluded because of negative plasma metanephrine results, 6-[\textsuperscript{18}F]fluorodopamine PET scans are consistently negative. These findings justify a clinical trial of 6-[\textsuperscript{18}F]fluorodopamine PET scanning as a diagnostic tool. (Hypertension. 2001;38:6-8.)

Key Words: fluorodopamine ▪ pheochromocytoma ▪ positron emission tomography ▪ metanephrines

Pheochromocytoma is a rare but clinically important tumor of chromaffin cells,\textsuperscript{1} characterized by production and secretion of catecholamines and often—but not always—hypertension. Most pheochromocytomas are benign, so that pheochromocytoma constitutes a form of surgically curable hypertension, and failure to diagnose the tumor can result in sudden, unexpected, and potentially lethal complications. Therefore, clinicians often wish to evaluate patients for pheochromocytoma, when hypertension and symptoms or signs suggest catecholamine excess.

Ideally, the diagnosis of pheochromocytoma using imaging techniques requires specific localization in tumor with a high sensitivity for tumor detection. Computed tomography (CT) and magnetic resonance imaging (MRI) have good sensitivity but poor specificity,\textsuperscript{2,3} and commonly available nuclear imaging modalities such as \textsuperscript{131}I-metaiodobenzylguanidine scintigraphy have high specificity but limited sensitivity.\textsuperscript{4–8}

Positron emission tomographic (PET) scanning is a physiology-based method of imaging, dependent on selective-binding or uptake and retention of radiopharmaceuticals by different tissues. The use of short-lived positron-emitting radionuclides allows administration of large tracer doses, resulting in high count density and superior resolution compared with that of single photon emitters. Because of rapid uptake of circulating catecholamines by chromaffin cells and rapid loss of their metabolites from the circulation, PET scanning can visualize a pheochromocytoma almost immediately after administration of 6-[\textsuperscript{18}F]fluorodopamine. In contrast, scintigraphy after administration of metaiodobenzylguanidine, which is not a catecholamine, requires imaging over 24 to 48 hours for optimal visualization.

6-[\textsuperscript{18}F]fluorodopamine, a sympathoneural imaging agent developed in the National Institutes of Health (NIH) intramural research program, is a positron-emitting analog of dopamine. In catecholamine-synthesizing cells, 6-[\textsuperscript{18}F]fluorodopamine is transported actively and avidly by both the plasma membrane norepinephrine transporter and the intracellular vesicular monoamine transporter. Accumulation of 6-[\textsuperscript{18}F]fluorodopamine-
derived radioactivity in catecholamine storage vesicles enables visualization of sympathetic innervation. Because chromaffin cells also express the plasma membrane and vesicular transporters, 6-[18 F]fluorodopamine might prove useful in diagnostic localization of pheochromocytoma.

Here we report the initial results of 6-[18 F]fluorodopamine PET scanning in patients with known or suspected pheochromocytoma. The goal was to test whether 6-[18 F]fluorodopamine PET scanning could correctly identify patients, who were known to harbor or to not harbor a pheochromocytoma, based on negative plasma levels of metanephrines. We viewed this as a necessary preliminary study to a more formal assessment of the diagnostic utility of this expensive and technically demanding modality.

Methods

Subjects

The subjects were 28 patients referred to the NIH for evaluation of known or suspected pheochromocytoma. All the patients gave informed, written consent to participate in the clinical protocol, which was approved by the Intramural Research Boards of the National Heart, Lung, and Blood Institute; the National Institute of Neurological Disorders and Stroke; or the National Institute of Child Health and Human Development.

Of the 28 patients, 9 had surgical confirmation of the tumor, 8 had previously diagnosed metastatic pheochromocytoma, and 11 had plasma levels of metanephrines that were within normal limits.

PET Scanning Procedure

Patients received 1 to 2 mCi of 6-[18 F]fluorodopamine intravenously over 3 minutes. Attenuation-corrected images were obtained, starting immediately after injection (15 minutes per position), using a GE Advance scanner. The duration of emission scanning was 8 to 15 minutes at each level. At least 1 transmission scan of 3 to 5 minutes duration was obtained at each level. The images were reconstructed using the MIRAGE program, which was developed by and is used routinely in the NIH Nuclear Medicine Department.

Data Analysis

The 6-[18 F]fluorodopamine PET scanning images were reviewed by K.P., D.S.G., J.A.C., and C.C.C. Only the latter 2 investigators were blinded to the plasma metanephrine levels or CT and MRI findings. Both blinded readers agreed in their observations with 1 exception: a patient for whom a diagnosis had not yet been established.

Results

Of the 9 patients with surgically proven pheochromocytoma, all had positive 6-[18 F]fluorodopamine PET scans that correctly indicated the location of the tumor (Figure 1).

Of the 8 patients with metastatic pheochromocytoma, all had positive 6-[18 F]fluorodopamine scans that showed ≥1 extra-adrenal tumor (Figure 2).

Of the 11 patients with normal plasma levels of metanephrines, 9 patients had negative 6-[18 F]fluorodopamine PET scans, 1 had extra-adrenal localization of 6-[18 F]fluorodopamine-derived activity medial to the left kidney and in the region of the tail of the pancreas, and 1 had essentially symmetric uptake of 6-[18 F]fluorodopamine in the adrenal areas. Neither of the latter 2 patients had surgical confirmation of these sites of 6-[18 F]fluorodopamine uptake.

Discussion

The present results demonstrate the ability of 6-[18 F]fluorodopamine PET scanning to detect and localize pheochromocytoma.

Other positron-emitting imaging agents have been used to visualize pheochromocytoma, including 18 F-fluorodeoxyglucose and 11 C-hydroxyephedrine. Uptake of the metabolic substrate 18 F-fluorodeoxyglucose by cells with a relatively high metabolic rate can lead to successful visualization of pheochromocytoma. However, in general, rapidly metabolizing cells take up 18 F-fluorodeoxyglucose, so this agent cannot detect pheochromocytoma specifically. One might expect that a sympathomimetic amine, such as 11 C-hydroxyephedrine, would have greater specificity than 18 F-fluorodeoxyglucose, because of the requirement for visualization of uptake by the plasma membrane and intracellular vesicular monoamine transporters. 11 C-Hydroxyephedrine PET scanning can detect pheochromocytoma rapidly (in 2 to 5 minutes) and clearly in most but not all patients, visualizing more lesions with better contrast than by using 131 I-metaiodobenzylguanidine.

The present study had a few limitations. First, there were insufficient numbers of patients to calculate diagnostic sensitivity and specificity. Second, 2 of the investigators (D.S.G. and C.C.C.) were blinded to the plasma metanephrine levels or CT and MRI findings. Both blinded readers agreed in their observations with 1 exception: a patient for whom a diagnosis had not yet been established.

Figure 1. Reprojected 6-[18 F]fluorodopamine PET scan in a patient with a left adrenal pheochromocytoma. The image was rotated ~20 degrees from coronal clockwise toward the viewer to delineate the tumor. The circle surrounds the tumor.

Figure 2. Midline sagittal 6-[18 F]fluorodopamine PET scan in a patient with pheochromocytoma and multiple bony metastases. The dotted line indicates the approximate location of the spine.
and K.P.) reviewing the scans were not blinded to the diagnosis, introducing the possibility of observer bias. Third, in the present study, the PET scanning results were not registered with MRI or CT. Such coregistration may facilitate anatomical distinguishing of the right adrenal gland from the head of the pancreas and the left adrenal gland from the tail of the pancreas. Fourth, only very limited views were obtained in several early patients, whereas more complete views of the chest and abdomen were obtained in most of the later patients.

In the present study, 6-[18 F]fluorodopamine PET scanning detected pheochromocytoma in all patients known to harbor the tumor. Of the 11 patients with negative plasma metanephrines, 9 also had negative 6-[18 F]fluorodopamine scans, and in the remaining 2 patients, we do not yet know if the positive 6-[18 F]fluorodopamine scan results indicate pheochromocytoma.

Based on the present results, we suggest that 6-[18 F]fluorodopamine PET scanning may prove to be a useful diagnostic test in patients with pheochromocytoma. Further study is needed to determine the extent of its usefulness, particularly in patients in whom biochemical testing is positive but CT and MRI are negative, and when biochemical results are negative but 6-[18 F]fluorodopamine PET scanning results are positive.

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References
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