

PET Imaging of Adrenal Cortical Tumors with the 11β -Hydroxylase Tracer ^{11}C -Metomidate

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The purpose of the study was to evaluate PET with the tracer ^{11}C -metomidate as a method to identify adrenal cortical lesions.

Methods: PET with ^{11}C -metomidate was performed in 15 patients with unilateral adrenal mass confirmed by CT. All patients subsequently underwent surgery, except 2 who underwent biopsy only. The lesions were histopathologically examined and diagnosed as adrenal cortical adenoma ($n = 6$; 3 nonfunctioning), adrenocortical carcinoma ($n = 2$), and nodular hyperplasia ($n = 1$). The remaining were noncortical lesions, including 1 pheochromocytoma, 1 myelolipoma, 2 adrenal cysts, and 2 metastases. **Results:** All cortical lesions were easily identified because of exceedingly high uptake of ^{11}C -metomidate, whereas the noncortical lesions showed very low uptake. High uptake was also seen in normal adrenal glands and in the stomach. The uptake was intermediate in the liver and low in other abdominal organs. Images obtained immediately after tracer injection displayed high uptake in the renal cortex and spleen. The tracer uptake in the cortical lesions increased throughout the examination. For quantitative evaluation of tracer binding in individual lesions, a model with the splenic radioactivity concentration assigned to represent nonspecific uptake was applied. Values derived with this method, however, did show the same specificity as the simpler standardized uptake value concept, with similar difference observed for cortical versus noncortical lesions. **Conclusion:** PET with ^{11}C -metomidate has the potential to be an attractive method for the characterization of adrenal masses with the ability to discriminate lesions of adrenal cortical origin from noncortical lesions.

Key Words: PET; adrenal cortex; adrenal tumors; steroid synthesis; etomidate; 11β -hydroxylase

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With increasing use of abdominal imaging techniques such as CT, sonography, and MRI, accidentally detected masses at the site of the adrenals, so-called incidentalomas, are frequently revealed. Incidentalomas, reported to occur in 0.3%–4% of abdominal CT investigations (1–6), are in most instances benign adrenal cortical adenoma without clinical or biochemical manifestations of hormone excess (1–6). Some incidentalomas represent pheochromocytoma, metas-

tasis to the adrenal, or are of other nonadrenal origin. Presently available imaging methods are seldom capable of establishing a definite diagnosis regarding origin and potential malignancy of the lesion.

Therefore, patients with incidentaloma generally must undergo more or less extensive clinical and laboratory examinations, including analyses of catecholamines and cortical hormones in urine or serum. Patients with biochemical evidence of hormone excess are generally considered for surgery. Surgery is also often advocated for tumors exceeding 3–4 cm in diameter, to exclude presence of adrenocortical carcinoma, an exceedingly rare tumor that is most often detected when it has reached conspicuous size (7). Moreover, because the adrenocortical carcinoma must have started as a smaller lesion, follow-up is recommended for all cortical lesions regardless of size. Patients with nonfunctioning lesions may also require biochemical follow-up because of the possibility that these lesions become hyperfunctioning with time (7). To simplify diagnosis and follow-up of patients with incidentaloma, there is a need to develop methods that can discriminate cortical adenomas from other lesions, such as pheochromocytoma, cyst, lipoma, and metastasis. Imaging methods with the ability to identify adrenocortical masses could also be used to visualize metastases from adrenocortical carcinoma.

Scintigraphy with the 6β -iodomethyl-19-norcholesterol analog (NP-59) was initially reported to exhibit rather high accuracy in identifying tumors of adrenal cortical origin (8–12), but has been less and less advocated because it has been time consuming and the accuracy has depended on the size of the tumor (13).

With the aim of providing a new method for identification of adrenal cortical lesions, we previously initiated studies in vitro and in animals using ^{11}C -etomidate and ^{11}C -metomidate (14). Etomidate, an imidazole-based ethyl ester, has been used as an anesthesia-induction agent, but has also been documented as a potent inhibitor of 11β -hydroxylase (15–18), a key enzyme in the synthesis of cortisol and aldosterone within the adrenal cortex. Metomidate, the corresponding methyl ester, has similar properties. Our previous studies, using frozen section autoradiography, showed that ^{11}C -etomidate and ^{11}C -metomidate had very high uptake in adrenal cortex and adrenal cortical tumors but

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low uptake in other examined organs, except the liver (14). In vivo PET studies in monkeys demonstrated high uptake and excellent visualization of the adrenal glands. Based on better synthetic characteristics, ^{11}C -metomidate was selected for further studies with the belief that this agent would be a good PET tracer for the characterization of adrenal masses. In the present work, we describe clinical ^{11}C -metomidate PET studies performed in patients with CT-verified adrenal masses planned for surgery.

MATERIALS AND METHODS

Patients

Fifteen patients with CT-detected adrenal masses >1 cm were included in the investigation. Two patients had clinical and biochemical signs of primary aldosteronism, and the remaining patients had incidentaloma. No patient was treated with chemotherapy or with medication that could interfere with 11β -hydroxylase. This study was accepted by the local ethical and isotope committees, and informed consent was obtained from all patients.

Patient characteristics are described in Table 1. There were 9 women and 6 men (age range, 42–78 y). Based on hormonal evaluations, 2 patients with primary hyperaldosteronism and 2 with adrenal cortical carcinomas were known to have adrenal cortical lesions before the PET examination.

Thirteen patients underwent adrenal surgery after the PET examination, and 2 underwent sonography-guided adrenal core biopsy. When histopathologic diagnosis of each lesion had been established, the patients were divided into 4 categories: (1) adrenal adenomas ($n = 6$); (2) adrenal hyperplasia ($n = 1$); (3) adrenal carcinomas ($n = 2$); and (4) lesions not derived from the adrenal cortex ($n = 6$). Analyses of tracer uptake are presented as averages within these defined groups.

Chemistry

Preparation of the Precursor. (R)-1-(1-phenylethyl)-1H-imidazole-5-carboxylic acid (R28141, 22.8 mg, 105 μmol ; Janssen

Pharmaceutica, Beerse, Belgium) was weighed into a 5-mL glass vial. Water (2 mL) and methylene chloride (2 mL) were added, followed by tetra-*n*-butylammonium hydroxide (60 μL 1.5 mol/L aqueous solution, 90 μmol ; Aldrich, Stockholm, Sweden). The vial was equipped with a magnetic stirring bar, capped, and stirred for 18 h at room temperature. The organic phase was removed, passed through a MgSO_4 plug, and filtered into a flask. Solvent was removed in vacuo and the residue was dissolved in 2.2 mL dimethylformamide (Aldrich). Each of 8 oven-dried 0.8-mL glass high-performance liquid chromatography (HPLC) vials was charged with 250 μL of the resulting solution. The precursor vials were crimp-capped and stored at -25°C for up to 5 mo before use.

Synthesis of [O-Methyl- ^{11}C]Metomidate. [^{11}C]methyl iodide was transferred in a stream of nitrogen into the precursor vial described earlier. The vial was heated in a 130°C aluminum block for 7 min. The vial contents were diluted with 0.5 mL water and purified by HPLC (Ultrasphere ODS [Beckman Industries, Stockholm, Sweden]; 5 μm , 10×250 mm; 45% ethanol; 55% water; 4 mL/min; 254 nm mass detection; radioactivity detection) and [O-methyl- ^{11}C]metomidate was collected from about 9 to 11 min. The product was formulated directly by diluting a 1-mL aliquot of HPLC eluent with 8 mL phosphate buffer, sterile-filtering the final solution. The product was analyzed by analytical HPLC for concentration of metomidate and radiochemical purity (Ultrasphere ODS [Beckman]; 5 μm , 4.6×250 mm; 60% 50:7 acetonitrile:water; 40% 50 mmol/L ammonium formate, pH 3.5; 1 mL/min; 254 nm mass detection; radioactivity detection; t_R [metomidate standard] = 5.2–5.3 min).

PET Investigations

Each patient was placed on the bed of the PET camera (GE 4096; Uppsala, Sweden) (19), and a short transmission scan was made to identify the diaphragm. Guided by the CT images, the 10-cm field of view of the PET camera was then centered to properly include the adrenal mass. A 10-min transmission scan was obtained using a rotating external ^{68}Ge rod source. These data were later used for the correction of attenuation in the emission scans.

TABLE 1
Patient Characteristics

Patient no.	Sex	Age (y)	Tumor size on CT	Location	Hormonal evaluation	Pathology
1	F	46	4 × 5 cm	LA	Negative	Adrenal adenoma
2	F	48	4 × 4 cm	LA	Negative	Adrenal adenoma
3	F	50	4 × 5 cm	RA	Negative	Adrenal adenoma
4	M	43	2 × 2.5 cm	LA	Primary aldosteronism	Adrenal adenoma
5	M	42	1.5 × 2 cm	LA	Primary aldosteronism	Adrenal adenoma
6	F	64	4 × 4 cm	RA	Increased catecholamines	Adrenal adenoma
7	F	59	1.8 × 2 cm	LA	Increased catecholamines	Cortical hyperplasia
8	M	52	4 × 5 cm	LA	Increased cortical hormones	Adrenal carcinoma
9	M	70	7 × 8 cm	RA	Increased cortical hormones	Adrenal carcinoma
10	F	64	1.5 × 3 cm	RA	Increased catecholamines	Pheochromocytoma
11	M	66	8 × 10 cm	RA	Negative	Myelolipoma*
12	M	74	4 × 5 cm	LA	Negative	Mesenchymal tumor*
13	F	68	10 × 15 cm	RA	Negative	Metastasis
14	F	55	3 × 3 cm	RA	Negative	Cyst
15	F	78	4 × 4 cm	RA	Negative	Cyst

* Histopathologic examination performed on core biopsy.

LA = left adrenal; RA = right adrenal.

Simultaneously with the intravenous injection of 294–938 MBq (average, 687 MBq) ^{11}C -metomidate in an arm vein, a dynamic imaging sequence was started, consisting of 14 frames with acquisition lengths from 1 to 10 min and a total examination time of 45 min. In some patients, 1 or 2 additional frames were obtained. Each frame consisted of 15 tomographic slices with a separation of 6.5 mm and an in-plane resolution of 5 mm (19). During the investigations, 12 blood samples were taken from an intravenous needle in the opposite hand, and radioactivity concentration was measured in whole blood and plasma.

Evaluation of Data

In the PET images, regions of interest (ROIs) were outlined to represent the following areas: a hot spot area in the tumor; a hot spot area in the normal adrenal gland; an average liver volume; an average spleen volume; an average stomach volume; and an average kidney cortex volume. For each of these areas or volumes and for each time frame, the average radioactivity concentration was calculated. These data were further recalculated to represent standardized uptake value (SUV) by dividing the radioactivity concentration by the ratio of total given radioactivity and total body weight, and SUVs were plotted as time–activity curves. These time–activity curves were averaged for all normal tissues throughout the whole group and for the different categories of adrenal cortical lesions as specified previously. To illustrate the differential tracer uptake pattern in the tumors and adrenals compared with the liver, the tumor-to-liver ratio and adrenal-to-liver ratios were calculated and plotted versus time after injection.

In an attempt to standardize for the fact that the plasma radioactivity and its kinetics might differ between patients, the Patlak graphical method (20) was used. With this method, the ratio:

$$Y = Ct(t)/Cp(t),$$

was plotted against a modified time:

$$X = \int Cp(\tau) d\tau / Cp(t),$$

where $Ct(t)$ = tissue concentration of radioactivity at time t and $Cp(t)$ = plasma radioactivity concentration at time t . For a tracer with irreversible binding, this graphical method typically results in a linear increase of specific tissue radioactivity (Y) with time (X), after an initial distribution phase, whereas tissue radioactivity remains constant for a tracer with rapid reversible binding. The method simulates the uptake temporal pattern that would result from a plasma radioactivity concentration, which is constant with time.

Because the generated Patlak plots clearly demonstrated that plasma is not valid as a reference, the same graphical method was applied with the spleen radioactivity concentration as a reference.

RESULTS

In the ^{11}C -metomidate PET images acquired during the first minutes after injection, the kidneys and pancreas were readily identified (Fig. 1). After a few minutes, however, these structures could no longer be seen and, instead, high uptake was noted in adrenal tumors and normal adrenals as well as in the liver. A high uptake was also seen in the stomach. Visually, all lesions that were later proven to represent adrenal cortical adenoma or cancer, as well as all normal adrenals, were characterized by high uptake (Figs. 1

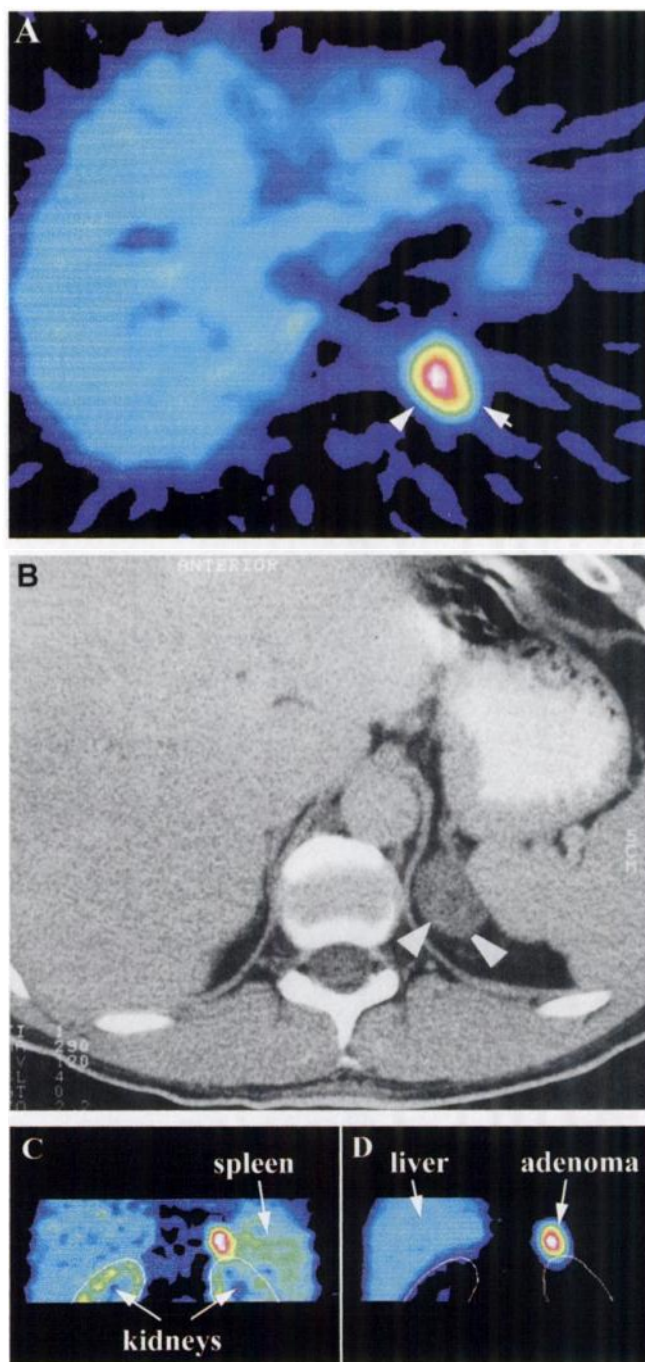


FIGURE 1. Patient with adrenal adenoma examined with PET and ^{11}C -metomidate. (A) In image obtained 30 min after injection of tracer, adenoma is clearly visualized (arrows). (B) CT scan of same section. (C) In coronal section through lesion and kidneys obtained 1 min after injection of tracer, these structures and spleen are well identified (D), whereas in same coronal section at 30 min after injection highest uptake is observed in adenoma.

and 2). In contrast, lesions subsequently proven to represent cyst, pheochromocytoma, or metastasis had low uptake and could not be discriminated from background (Figs. 3 and 4). The adrenal carcinomas had irregular and generally lower ^{11}C -metomidate uptake than the adenomas. Three patients suspected to have pheochromocytoma because of slightly

increased levels of urinary catecholamines, had high ^{11}C -metomidate, indicating the presence of adrenocortical tumor, subsequently verified by surgery and histopathology.

The time-activity curves of the spleen and kidney were similar, with a peak SUV of about 10 reached within a few minutes after injection, after which the SUV rapidly decreased to about 1–2 (Fig. 5A). The liver uptake was variable with peak values of 7–18 (average, 12) reached within about 10 min, followed by a slight decrease to 6–20 (average, 11). In 3 patients, liver uptake increased during the whole study. In the normal adrenals, the uptake increased rapidly during the first minutes up to SUV of 7–17 (average, 12), followed by a further slow increase up to 9–22 (average, 16). The right adrenals, on average, had 20% higher uptake than the left adrenals. The adrenal adenomas and carcinomas showed a kinetic pattern similar to the normal adrenals, with final SUVs of 17–55 (Fig. 5B).

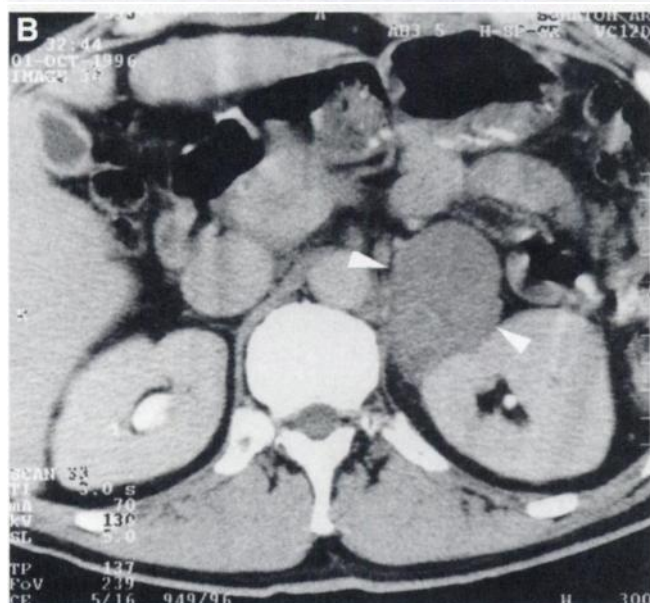
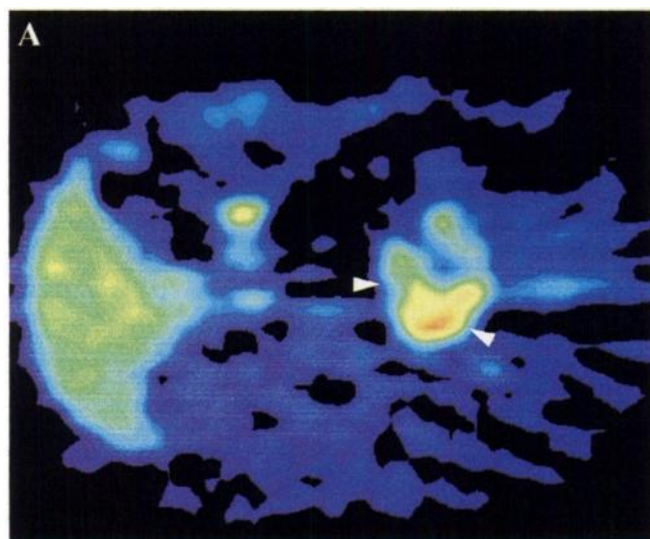


FIGURE 2. Patient with adrenal cancer examined with PET (A) and CT (B). Tumor with irregular uptake is well visualized.

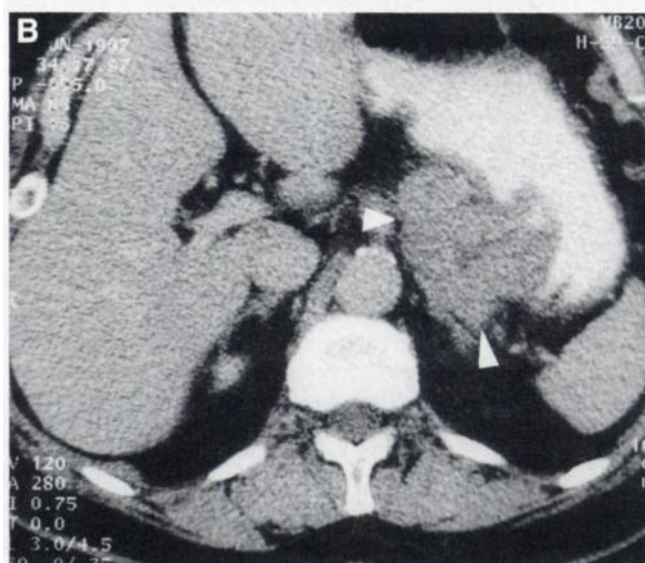
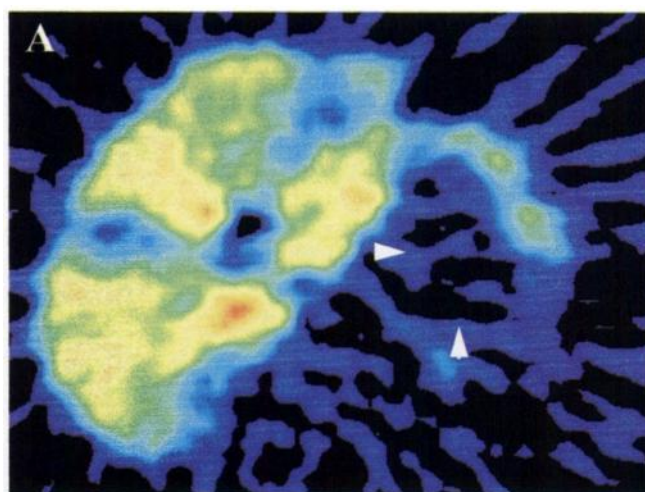


FIGURE 3. Patient with metastasis investigated with PET and ^{11}C -metomidate (A) and CT (B). Tumor (arrows) has low uptake.

The tumor-to-liver ratios had a minimum of about 1.5 after 3–5 min, followed by a slow increase to between 1 and 3.5 (average, 2.0). No significant differences were noted between tumor-to-liver and adrenal-to-liver ratios.

The Patlak graphical method, in which plasma radioactivity was used as the input function, applied to normal adrenals and adrenocortical tumors, showed a curvilinear increase with time with large intersubject variations. The same method applied to the spleen and kidneys showed a significant decrease starting from 3 min after injection to the end of the study.

When the spleen radioactivity data were used as the input function for the Patlak graphs, only slightly curved increases with time were found in normal adrenals and adrenocortical tumors (Fig. 6). The liver showed a biphasic uptake pattern with an initial phase similar to the adrenals and a later phase with a decreased slope. Kidney uptake was almost constant with time. As a quantitative measure of uptake, the uptake at the last time point was divided by the area under the curve of

the spleen. This measure was then compared with the SUV at the last time point. These 2 measures were highly correlated among all adrenal cortical lesions and normal adrenals ($R^2 = 0.93$). For this reason, the SUVs were

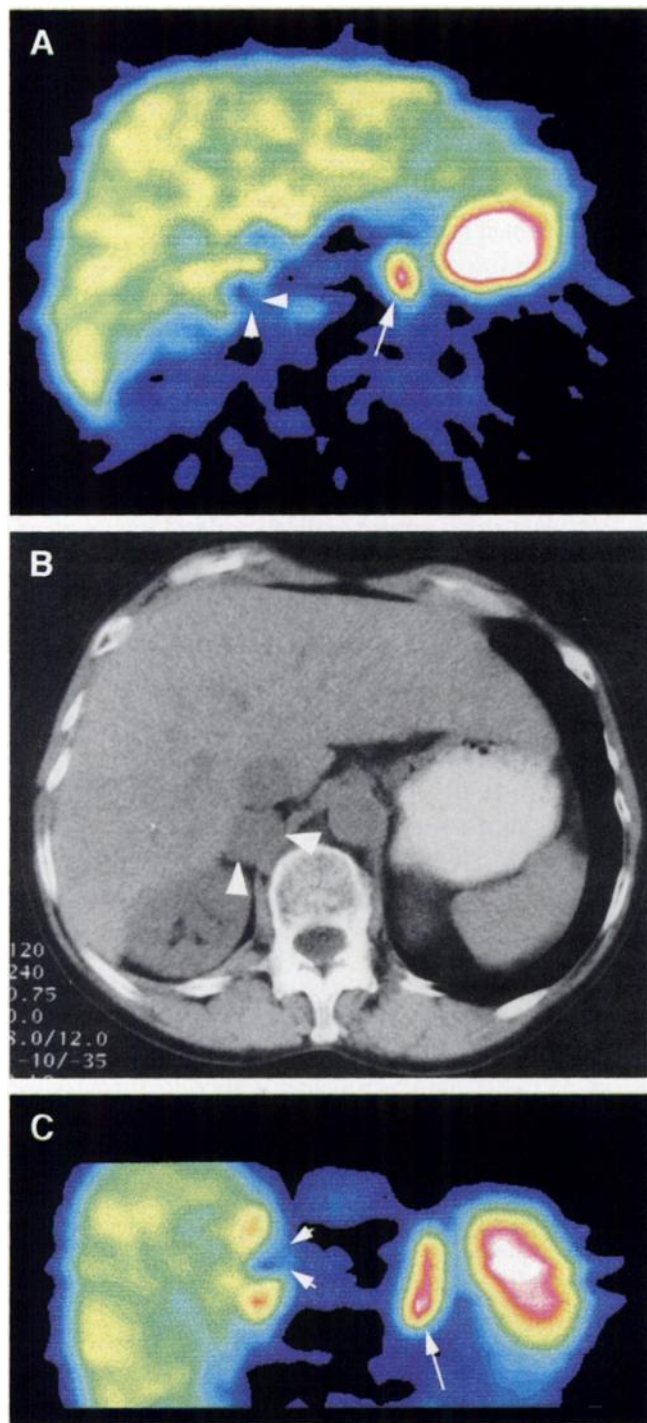


FIGURE 4. Patient with pheochromocytoma, examined with PET in axial section (A) and with CT (B). Tumor has low uptake (short arrows), whereas normal contralateral adrenal gland has high uptake (long arrow). Coronal section through adrenal (C) shows low uptake in pheochromocytoma surrounded by displaced adrenal cortex. Normal adrenal gland is indicated by long arrow.

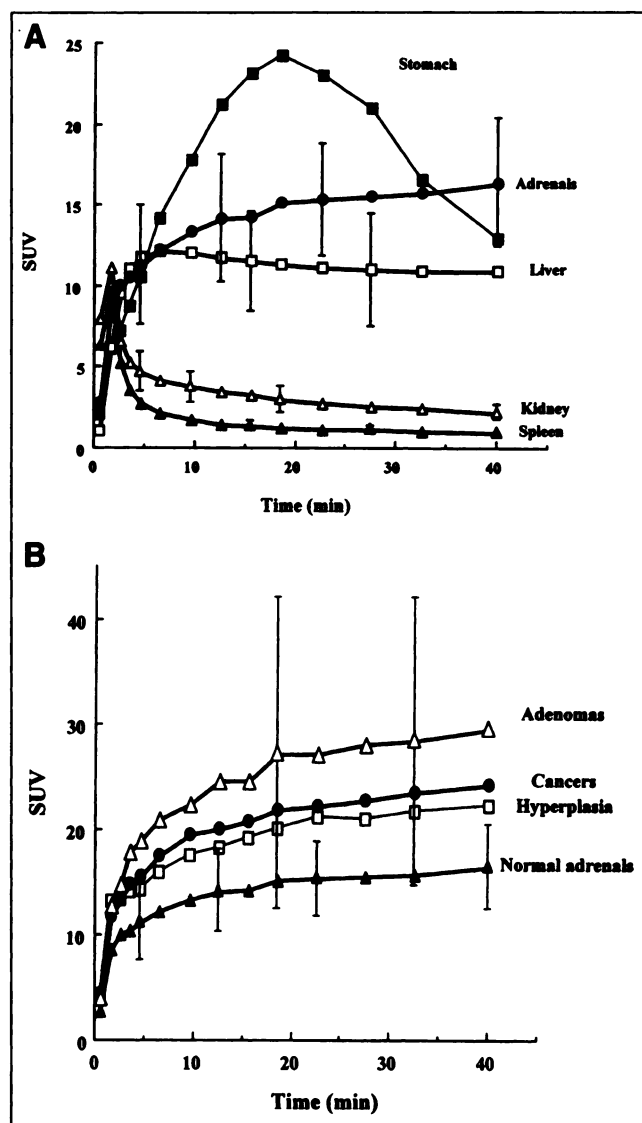


FIGURE 5. Uptake kinetics of ^{11}C -metomidate in different normal tissues (A) and in different adrenal lesions (B). Tracer concentration given as SUV. Highest uptake is observed in stomach, followed by adrenals. Kidney and spleen have low uptake, especially at late time points. Adrenals and adrenocortical lesions show increased uptake with time throughout examination.

regarded as sufficient for a quantitative comparison between different types of lesions (Fig. 7). The highest uptake was seen in adenomas (average, 29; SD, 14; $n = 6$), followed by cancers (average, 23; $n = 2$), hyperplasia (average, 22; $n = 1$), and normal adrenal glands (average, 16; SD, 4; $n = 11$). The liver had lower uptake (average, 11; SD, 4; $n = 14$), and the miscellaneous other lesions had much lower uptake (average, 1.5; SD, 0.7; $n = 6$).

Plasma radioactivity showed a peak within the first few minutes, followed by a rapid decrease down to an almost constant level during the remaining time. The SUV of plasma was about 1 at the end of the experiment. The plasma-to-whole blood ratio was basically constant over the experimental period at a level of 1.2.

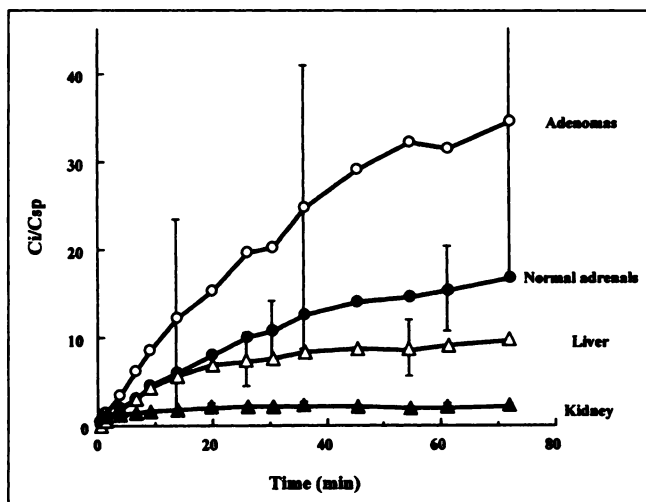


FIGURE 6. Patlak graphical representation of tracer uptake, using tracer concentration in spleen as reference. Uptake ratios show increase with time for adenomas and normal adrenals, whereas liver uptake and kidney uptake seem to reach plateaus.

DISCUSSION

The purpose of this study was to evaluate whether PET with ^{11}C -metomidate could be used as a clinical tool for the differential diagnosis of adrenal masses previously identified by conventional radiology. Because a majority of incidentalomas are known to be of adrenocortical origin, we wanted to find a tracer that would positively identify such lesions, rather than a tracer specific for metastases or pheochromocytomas. For this reason, it was logical to seek potential tracers

in the biochemical pathways of the adrenal cortex steroid synthesis. We found a good candidate in ^{11}C -metomidate, a tracer that can be synthesized in adequate quantities for high-quality PET studies, showing excellent binding with high selectivity for adrenal cortex *in vitro* and having favorable kinetics with essentially irreversible binding within the timespan of a PET study (14).

Etomidate and metomidate are known as highly potent inhibitors of 11β -hydroxylase, and our previous *in vitro* studies demonstrated an excellent correlation between degree of binding to adrenal tumors *in vitro* and their staining for an antibody raised against 11β -hydroxylase (14).

In the limited number of patients presented in this study, we document very high uptake in normal adrenals and adrenal adenomas as well as in 2 adrenocortical carcinomas. All lesions of nonadrenocortical origin had such low uptake that they could not be discriminated from surrounding tissues. Thus, this pilot study indicates that PET with ^{11}C -metomidate may provide accurate differential diagnosis in patients with adrenal masses. However, a final assessment of the accuracy of this new method can be made only when a larger patient group has been investigated and analyzed.

The potential role of PET and ^{11}C -metomidate in clinical practice must also be judged in relation to other available diagnostic methods. CT and MRI are excellent imaging methods and are usually the basis for the diagnosis of an adrenal mass. Their major drawback is the lack of specificity. Currently the differential diagnosis of adrenal masses is generally based on hormonal or catecholamine evaluation, which is reliable only in cases of steroid hormone or catecholamine excess.

Scintigraphy with NP-59 has been reported to have high specificity and 90%–95% accuracy for identification of adrenocortical lesions (12). A drawback of the NP-59 method is that the images are obtained as late as 4–7 d after tracer injection. Such long times are needed to achieve a sufficiently high lesion-to-background ratio. Another drawback is that glucocorticoids must be given for a few days before and after the tracer administration to suppress the normal adrenal uptake.

We could find only 2 publications on the use of PET for the study of adrenal tumors. Boland et al. (21) and Erasmus et al. (22) showed that PET with FDG had high accuracy in defining malignant tumors at the site of the adrenals. However, high uptake was noted only in metastases from primary tumors at other sites, whereas all adrenal adenomas had low uptake. Because of the limited specificity of the other imaging methods, we are suggesting that ^{11}C -metomidate PET should be used as 1 of the first methods in the evaluation of adrenal incidentalomas. The very high contrast of adrenocortical lesions and the sustained high uptake from 20 min after injection should allow multiple fields to be acquired with good image quality. Such a larger coverage of the body could be advantageous in the search for metastases from adrenocortical cancers.

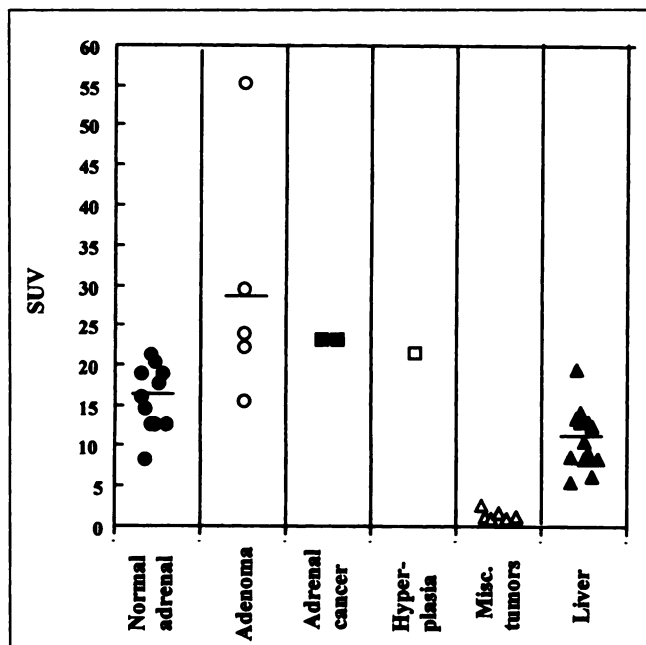


FIGURE 7. Final SUVs of different categories of lesions and normal tissues. Adrenocortical lesions have highest uptake values, followed by normal adrenals and liver. Nonadrenocortical tumors have low uptake.

For quantitation of the binding of ^{11}C -metomidate to adrenal 11β -hydroxylase, we have used a few different methods, one of which was to measure the SUV, which includes compensations for differences in amount of given radioactivity and in patient body weight. In view of the fact that the uptake kinetics reached a plateau at the end of the study, this method has some bearing. This method, however, assumes that the tracer kinetics in blood are equal in all individuals. Within the PET field, it is common to show uptake kinetics by applying the Patlak graphical method (20), which is corrected for differences in plasma or reference tissue kinetics. When this method was used to describe the ^{11}C -metomidate uptake, with plasma radioactivity concentration as input, a nonlinear uptake was seen, with large variations between individuals. The same method applied to renal cortex or spleen showed a marked reduction with time, strongly indicative of the presence of metabolites that lack binding or show a different binding pattern. For this reason, we do not recommend this latter method. We have performed further analyses on the metabolite spectrum in plasma (T. Bonasera, unpublished data, 1998), which have indicated rather complex conditions with a rapid metabolism, leading to a dominance of metabolites in protein free plasma, but with intact tracer bound to plasma proteins. When spleen tissue was used as a reference, more reasonable Patlak plots were obtained, with less curvature in the adrenal tissues and with a plateau reached in the renal cortex. The choice of this tissue as a reference was also based on results from previous in vitro studies that showed absence of binding in splenic tissue from rats and pigs. Furthermore, this tissue has a high perfusion similar to the adrenals. The slight curvature observed with this plot could relate to the fact that the spleen may also contain significant amounts of metabolites at later time points. In vitro studies have shown that the rate of dissociation of binding to the adrenal cortex is very low (14). With several assumptions, which must be tested further, the slope of the Patlak graph should be proportional to the concentration of the 11β -hydroxylase enzyme within a specified ROI. By outlining the full adrenals or the tumors with a margin to enclose the whole gland or tumor, an estimate of the total amount of enzyme could be attained.

An important implication from the shape of the Patlak curves of the adrenals is that the dissociation must be slow in vivo. In the liver, a different kinetic profile is observed, suggesting that the uptake in this organ might be mediated through systems other than 11β -hydroxylase. Possible candidates include other P450-enzymes. This opens up possibilities to enhance the discrimination of adrenal lesions from normal liver in the ^{11}C -metomidate PET study by temporarily blocking liver enzymes with appropriate drugs.

The high uptake in the stomach is probably mediated through a different mechanism. Initially after injection, an increasing uptake is seen in the stomach wall, whereas the central portion has low uptake. After about 20 min, a marked increase is seen centrally in the stomach, which in some

patients is decreased markedly by the end of the study. A likely explanation for this uptake is that ^{11}C -metomidate is protonated in the stomach's acidic environment and trapped in the gastric juice. It might therefore be possible to reduce the stomach uptake with omeprazole or other agents that reduce the acidification process.

The data obtained in our previous study (14) showed that ^{11}C -metomidate is an indicator of 11β -hydroxylase tissue content and that high expression of this enzyme is the basis for visualization by ^{11}C -metomidate PET. Because high uptake was also observed in adrenocortical adenomas, which are hormonally silent, it is apparent that the enzyme expression is not the factor governing the lack of hormone synthesis. This is advantageous for our application, because silent adenomas constitute the largest group of incidentalomas and these are the ones that often fail to be correctly diagnosed by blood analyses.

CONCLUSION

This study indicates that PET with ^{11}C -metomidate has a promising potential to be used clinically for characterization of adrenal masses and that it positively identifies lesions of adrenocortical origin.

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