SPECIAL CONTRIBUTION

Diagnostic Accuracy and Pitfalls of [Iodine-131]6-Beta-Iodomethyl-19-Norcholesterol (NP-59) Imaging

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NP-59 concentrates in steroid hormone synthesizing tissues, enabling scintigraphic localization and characterization of endocrine dysfunction in the adrenal cortex and ovary. Studying 108 consecutive cases from 1982 to 1985 and using clinical, biochemical, radiographic, and pathologic data, we performed a rigorous assessment of the accuracy and pitfalls of NP-59 scintigraphy. The evaluation was divided into categories of abnormal hormone secretion: Cushing's syndrome, primary aldosteronism, and hyperandrogenism. Additional categories included euadrenal tumors (without detectable hormone dysfunction) and sites of residual adrenal cortical tissue. The accuracy of NP-59 scintigraphy ranged from 71% in primary aldosteronism and 75% in euadrenal tumors, to 100% for Cushing's syndrome and hyperandrogenism. However, more than in most nuclear medicine studies, NP-59 imaging requires well-defined indications to be met for it to be efficacious, including the fulfillment of clear clinical, biochemical, and radiographic criteria. The high reproducibility of NP-59 scintigraphic interpretation was demonstrated when 40 random cases underwent interinstitutional exchange and through interobserver evaluation at the University of Michigan. Responses of 85/126 medical centers to questionnaires revealed the high level of NP-59 safety.

J Nucl Med 1990; 31:526–534

The radiolabeled cholesterol analog, [iodine-131]6-beta-iodomethyl-19-norcholesterol (NP-59), concentrates in steroid hormone synthesizing tissues such as the adrenal cortex and some ovarian tumors (*1*). Localization enables scintigraphic definition of the sites of steroid hormone synthesis and conclusions concerning the functional nature of tumors in these sites. Previous reports have described the diagnostic value of scintigraphic images made with NP-59 in defining the sites of hormone synthesis in Cushing's syndrome (*2,3*), primary aldosteronism (*4–10*), and hyperandrogenism (*11–14*). In addition, scintigraphy has demonstrated that incidentally discovered adrenal tumors not associated with excess hormone production (euadrenal tumors) can often be categorized as concentrating or not concentrating NP-59, a characteristic that distinguishes between benign and malignant tumors (*15–17*). Occasionally NP-59 scintigraphy has been employed to determine if and where residual adrenal cortical tissue resides after disease or surgical intervention (*18*).

Although NP-59 images have clearly been helpful in the diagnosis of selected patients, adrenal scintigraphy has not been rigorously evaluated for its diagnostic accuracy in patients routinely referred for study. By examining 108 consecutive cases, the accuracy of NP-59 scintigraphy in its multiple applications was evaluated, and equally important, the pitfalls were delineated. Together with interobserver variation in the above cases, an additional 40 random cases exchanged with a second institution were reviewed to determine the accuracy of image interpretation. Finally, a survey of NP-59 users was made to assess the safety of this radiopharmaceutical.

MATERIALS AND METHODS

At the University of Michigan we planned to evaluate the clinical, biochemical, and radiographic data with the results of NP-59 scintigraphy in 100 consecutive cases. To ensure sufficient number, 108 consecutive studies performed from 1982 to 1985 were reviewed. A number of these cases have been reviewed in previous publications (*5,15,16,19,20*). Each study was reviewed independently by three nuclear medicine specialists (JCS, BS, and MDG), knowledgeable of adrenal disorders and imaging. All patients received a 1-mCi i.v. injection of NP-59 and dulcolax tablets during imaging to reduce overlying colonic activity. In addition, all patients studied for hyperaldosteronism and hyperandrogenism received 5 mg of oral dexamethasone per day starting 7 days prior to injection and ending on the last day of imaging, to suppress corticosteroid synthesizing tissue. Images were obtained at 5–7 days postinjection, except in cases of hyperal-

Received July 7, 1989; revision accepted Nov. 16, 1989.

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dosteronism, where imaging at 3–5 days following injection was designed to detect the earliest appearance of adrenal activity.

The review was conducted in three stages. The first stage analyzed images in the absence of clinical and biochemical data, emphasizing symmetry of adrenal NP-59 concentration and the earliest day after injection when concentration could be discerned, to determine if disagreements in diagnostic decisions were related to interpretation of the pictorial data. In the second stage, the clinical, biochemical, and radiographic data available at the time of imaging were reviewed with the images to render a diagnosis. In the final stage, correlations were made of all data obtained before and after each study (including responses to requests sent to referring physicians for follow-up data) to arrive at a final diagnosis.

It became apparent that the diagnostic decisions and final diagnoses required definitions of the possible disorders to guide the interpretation of scintigraphic images, and that such definitions had not been previously established for this purpose. Using standard textbooks of endocrinology (*21,22*), definitions of Cushing's syndrome, primary aldosteronism and hyperandrogenism were devised to be used as scintigraphic guidelines (Tables 1–3). Euadrenal tumors were defined as anatomic adrenal gland enlargement when there was sufficient evidence to conclude that no adrenal hormone was secreted in excess. Five cases not referred for clinical questions were excluded from the review, leaving 103 cases for analysis (Table 4).

The clinical usefulness of NP-59 scintigraphy is defined in terms of accuracy at determining the site(s) of corticosteroid hormone synthesis, subsequently interpreted in light of the clinical question asked by the referring physician. Questions

TABLE 1
Criteria for Cushing's Syndrome

A. Diagnosis of Cushing's syndrome
  1. Clinical
    a. Hypertension
    b. Obesity: centripetal, facial
    c. Stria: purple
    d. Virilization in the syndrome
    Should have *at least one* of the clinical features, *and*
  2. Laboratory
    a. Evidence of cortisol excess
      1. High normal or high plasma cortisol (>25 μg/dl in a.m.) *or*
      2. Lack of diurnal variation in plasma cortisol *or*
      3. Elevated rate of excretion of free cortisol (>125 μg/24 hr) *or*
      4. Elevated rate of excretion of 17-hydroxysteroids (>10 mg/24 hr), *and*
    b. Evidence of altered control of cortisol secretion
      1. Failure to suppress plasma cortisol to <15 μg/dl, preferably failure to suppress to <5 μg/dl by
        a. 1 mg dexamethasone in evening *or*
        b. 4 (or 16) mg of dexamethasone over 48 hr, *or*
      2. Failure to suppress urine 17-hydroxysteroids to less than half of basal by 4 (or 16) mg of dexamethasone over 48 hr.
B. Location of primary abnormality in Cushing's syndrome
  1. Pituitary
    a. Plasma ACTH >90 pg/ml (in a.m.), *and*
    b. Either
      1. Evidence of pituitary adenoma by CT or by removal *or*
      2. Presumptive by absence of evidence of ectopic source of ACTH (by chest x-ray or other means), *or*
    c. Suppression urine (or plasma) cortisol by 16 mg/d but not by 4 mg/d of dexamethasone over 2 days.
  2. Ectopic ACTH or CRH
    a. Plasma ACTH >90 pg/ml, *and*
    b. Tumor secreting ACTH or CRH from
      1. measurement of ACTH or CRH in blood of vein from tumor, *or*
      2. measurement of hormones in tumor *or*
      3. relief of clinical and laboratory abnormalities of the syndrome upon removal of the tumor, *and*
    c. Lack of suppression of plasma cortisol by 16 mg/d of dexamethasone over 2 days.
  3. Adenoma
    a. Biochemical-image
      1. Lack of ACTH dependence by
        a. plasma ACTH <60 pg/ml (in a.m.), *or*
        b. Failure of plasma cortisol or urine 17-hydroxysteroids to suppress with 10 mg of dexamethasone over 48 hr; *and*
      2. Enlargement of one adrenal gland on CT or other image of anatomy, *or*
    b. Relief of clinical and laboratory abnormalities by removal of adenoma.
  4. Bilateral nodular hyperplasia
    a. Lack of ACTH dependence as described under B-2 c, *and*
    b. Bilateral morphologic abnormalities by
      1. CT or other image of anatomy, *or*
      2. histologically.
  5. Carcinoma

TABLE 2
Criteria for Primary Aldosteronism

A. Diagnosis of primary Aldosteronism
  1. Clinical
     Hypertension (usually without edema)
  2. Laboratory
     a. Usual entry evidence
        Hypokalemia
        —spontaneous, i.e., in absence of diuretics, *or*
        —difficult to repair by oral potassium with diuretics.
     b. More definitive criteria
        1. Plasma renin value is low and cannot be elevated by upright posture (walking) for 3 hr plus and/or injection of furosemide.
        2. Urinary aldosterone level is elevated and is not suppressed by
           —oral sodium, 200 mEq/d for 3 days, *or*
           —desoxycorticosterone injections.
  3. Interpretation
     —b 1) plus b 2) make the diagnosis definite.
     —Hypertension, hypokalemia, and a low renin value in upright position make the diagnosis probable.
     —Hypertension and hypokalemia make the diagnosis possible.
B. For confirmation of the type of primary aldosteronism, the following are required:
  1. Adenoma
     a. Definitive evidence
        1. Resection of an adenoma (by histology), *and*
           a. no evidence of abnormality in the contralateral adrenal gland on CT, *and*
           b. disappearance of hypertension *or* least disappearance of hypokalemia.
        2. Levels of aldosterone in blood from one adrenal vein that are twenty or more times higher than those in blood from the contralateral vein.
     b. As presumptive evidence is: tumor in one adrenal gland <2.5 cm in diameter when no operation has been performed.
  2. Bilateral hyperplasia
     a. Definite
        1. Either no abnormality or bilateral enlargement of adrenal glands on CT *and* decline in blood pressure and repair of hypokalemia by spironolactone treatment, *or*
        2. Equal (less than two-fold difference) *and* substantial concentrations of aldosterone in blood from the adrenal veins *and* decline in blood pressure and repair of hypokalemia by spironolactone treatment.
     b. Possible or probable: no nodule or tumor or more than borderline and equal enlargement of adrenal glands by CT.
  3. Carcinoma (rare but we have cases)
     Invasion of tissue by tumor as seen
     a. by surgeon *or*
     b. by pathologist *or*
     c. by angiography *or*
     d. by CT (which may show metastases).

of Cushing's syndrome, primary aldosteronism, and hyperandrogenism ask if the disease is in one or more sites; a single site usually signifying a potentially resectable tumor. For euadrenal tumors, the clinical question asks if there is evidence of function in the tumors, the implication being that a functioning tumor is more likely to be benign (*15*). The clinical question of residual adrenal tissue asks where the tissue resides. If the clinical questions were not properly formulated, then the accuracy of the scintigraphic procedure could not be assessed. Therefore, when in retrospect the clinical question was improper because the patient did not clearly have the indicated disease, the case was relegated to a group labeled Improper Question (Table 4).

Twenty randomly selected cases from the University of Michigan and 20 randomly selected cases from Victoria Hospital in London, Ontario were exchanged to determine interobserver variation in the interpretation of NP-59 scintigraphic images as unilateral, bilateral, or absent concentration. Three additional nuclear medicine physicians (AD, GAH, AGM) from Victoria Hospital carried out the review. In addition, agreement between the three University of Michigan interpreters was evaluated.

Questionnaires asking for information on adverse reactions were sent to 126 institutions using NP-59 to determine how many and what types of adverse reactions were experienced between April 1984 and September 1987. Adverse reactions were divided into three groups according to severity.

RESULTS

Accuracy

Cushing's Syndrome. Twenty-three cases were referred for the evaluation of Cushing's syndrome, however, in five instances clinical and biochemical data were insufficient to support the diagnosis. NP-59 scintigraphy rendered the correct diagnosis in the remaining 18 cases (100% accuracy) (Tables 4 and 5).

There were 12 cases of bilateral NP-59 adrenal concentration consistent with adrenal hyperplasia. Given that seven patients had elevated or nonsuppressible ACTH levels, the diagnosis of pituitary ACTH-dependent Cushing's syndrome was made (*2,21,22*). These patients had pituitary enlargement on CT and became

TABLE 3
Criteria for Hyperandrogenism

A. Diagnosis of virilization (adult women)
  1. Clinical
    a. Not specific but almost
      1. Hirsutism, more specific if florid and of few months duration
      2. Acne
    b. More specific of virilization (at least one feature should be present)
      1. Cliteromegaly
      2. Frontal balding
      3. Deepening voice
    c. Onset over weeks or few months.
  2. Laboratory
    a. Ovary
      1. Plasma total testosterone: >1 ng/ml usually >2 ng/ml; *or*
      2. Free testosterone elevation if total testosterone is not elevated *and*
    b. Adrenal (the tumors are usually large)
      1. 17-ketosteroids (urine) elevation, *and/or*
      2. DHEA-S (plasma) elevation, *and*
    c. LH and FSH. (Plasma) low levels.
    d. Caution
      1. Many patients with hirsutism do not have an endocrine cause for hair growth, and few have androgen-secreting tumors. For example the polycystic ovarian syndrome usually is associated with hirsutism, amenorrhea, and modest elevation in plasma testosterone (<2 ng/ml); a high LH and low FSH are also commonly seen in women afflicted with this disorder.
      2. Adrenal genital hyperplasia in adult cases typically will be associated with clinical virilization and increased 17-ketosteroids excretion. The diagnosis is supported by an elevation in the serum 17-hydroxyprogesterone levels.
      3. Cushing's syndrome may be associated with clinical virilization; usually there are other clinical manifestations of Cushing's syndrome and the criteria of Cushing's syndrome (Table 6) would be fulfilled.
B. Criteria for determining site(s) androgen production (tumor in the ovary may be small).
  1. Probable:
    a. CT or MRI or ultrasound evidence of tumor in ovary or adrenal, *or*
    b. Excised tumor appearing morphologically typical of an androgen secreting tumor.
  2. Definition
    a. Levels of the offending androgen in venous effluent of the adrenal gland or the ovary are much higher (>5-fold) than those from the contralateral gland, *or*
    b. Disappearance of clinical and biochemical abnormalities upon removal of the tumor.

well following pituitary adenoma resection. In the remaining five cases with bilateral NP-59 concentration and normal ACTH levels, the diagnosis of primary adrenal cortical hyperplasia was made (*19,21,22*). Four of these five patients underwent bilateral adrenalectomy confirming bilateral nodular hyperplasia and a single patient received chemotherapeutic ablation of adrenal hypersecretion with mitotane. All five patients were well on follow-up.

Three cases of early unilateral NP-59 concentration were interpreted as Cushing's syndrome secondary to adrenal adenoma. Following unilateral adrenalectomy, remission of clinical features confirmed the diagnosis (*2,21,22*).

The final three patients with Cushing's syndrome demonstrated no concentration of NP-59 in the region of either adrenal gland, representing adrenal cortical carcinoma. Malignant adrenal cortical carcinomas usu-

TABLE 4
Summary of Cases with Correct Diagnosis

Diagnosis	No. of cases	Improper question	No proof	Evaluated cases	No. NP-59 correct	% correct
Cushing's syndrome	23	5	0	18	18	100
Primary aldosteronism	27	6	7	14	10	71
Hyperandrogenism	10	8	0	2	2	100
Euadrenal tumors†	39	3	*	36	27	75
Residual adrenal tissue	4	*	4	*	*	*
Hyperestrogenism	1	1	*	*	*	*
Research cases	4	*	4	*	*	*
Total	108	23	15	70	57	86.5%

* Not applicable.
† See text.

TABLE 5
Site(s) of Hormone Excess in Cushing's Syndrome

Type of Cushing's	No.	Adrenal NP-59 concentration	No.
Pituitary	7	Bilateral	7
Nodular hyperplasia	5	Bilateral	5
Adrenal adenoma	3	Unilateral	3
Adrenal carcinoma	3	None	3
Scintigraphy correct:			18/18 or 100%

ally do not concentrate NP-59, either because function is low per unit mass or because cholesterol is synthesized de novo in the tumor (*15*). The excess production of cortisol suppresses ACTH secretion and consequently the function of the contralateral adrenal gland (*15,23, 24*). The tumors were delineated on CT and carcinoma confirmed at operation.

Primary Aldosteronism. Twenty-seven cases of primary aldosteronism were referred for evaluation (Tables 4 and 6). Six cases with insufficient data to support the diagnosis and seven additional cases without independent proof of the site of excess aldosterone production were omitted from the review. Accuracy in the remaining cases was 10/14 or 71%.

Only one of three cases of nodular hyperplasia exhibited bilateral NP-59 concentration (two of three interpreters) in enlarged adrenal glands containing 1-cm nodules (adrenalectomy). In another case, adrenal size was at the upper limits of normal on CT suggesting a bilateral disorder, but there was no appreciable concentration of NP-59 in the adrenal glands, characteristic of normal dexamethasone suppressed adrenal glands (*25*). In the third case, all three interpreters believed image quality was too poor to render a diagnosis.

Ten patients had adrenal adenomas (6 left, 4 right), 0.5–2.5 cm in diameter at resection, except for a single 0.8-cm adenoma on CT that has not been removed. In eight cases NP-59 images correctly located the unilateral site of the excess aldosterone production. However, in one patient all three interpreters identified bilateral NP-59 concentration, yet a 1×2-cm adenoma was resected and subsequently all clinical features (*21,22*) remitted. In another case, one interpreter correctly identified the location of a 0.5-cm left adrenal adenoma, while the remaining two investigators believed that the timing of the images was improper and the study was indeterminate. A right adrenal mass measuring 11×10×7 cm on CT demonstrated distorted NP-59 concentration and was held to be carcinoma, a diagnosis confirmed at operation.

Hyperandrogenism. Ten cases of hyperandrogenism were referred for evaluation. In the two cases meeting the defined criteria (Table 3), the accuracy was 100%. There was no radiotracer concentration on the side of a 12-cm right adrenal mass on CT consistent with the adrenal cortical carcinoma subsequently confirmed at adrenalectomy (*21,22,24*). In the second case, there was NP-59 concentration in the pelvis corresponding to the 3-cm left ovarian mass on ultrasound and CT and normal adrenal concentration. The interpretation that excess androgens arose from an ovarian tumor proved to be correct when a benign lipoid cell ovarian tumor, previously described as a cause of virilization (*26*), was resected.

Euadrenal Tumors. Thirty-nine patients were referred for the evaluation of euadrenal tumors discovered incidentally on CT. In two cases euadrenalism was not clearly established (*21,22*), and in a third case with normal symmetric NP-59 activity, MRI determined that the 4-cm mass did not involve the adrenal gland, leaving 36 for further study (Tables 4 and 7). The accuracy was 27/36 or 75%.

There were 18 cases of asymmetric increased NP-59 concentration in adrenal tumors measuring 1.7–5 cm in diameter on CT. Dissent among interpreters occurred when a single interpreter believed NP-59 concentration was symmetric in one case. Tissue diagnosis obtained in four cases revealed corresponding unilateral nodular hyperplasia at autopsy and three adenomas at adrenalectomy. The remaining patients had no tissue diagnosis, but were alive and well 2–6 yr later.

NP-59 concentration was decreased or distorted in nine euadrenal tumors, six measuring >5 cm in diameter by CT and/or resection. The other three cases included a 2-cm adrenal tumor without tissue diagnosis, a 1-cm tumor in a patient with MEN-1 syndrome corresponding to nodular hyperplasia at adrenalectomy, and a small adrenal mass without tissue diagnosis in a

TABLE 6
Site(s) of Hormone Excess in Primary Aldosteronism

Type of aldosteronism	No.	Adrenal NP-59 concentration	No.
Nodular hyperplasia	3	Bilateral	1
		Indeterminate	2
Adenoma	10	Unilateral	8
		Bilateral	1
		Indeterminate	1
Carcinoma	1	Distortion of one gland	1
Scintigraphy correct:			10/14 or 71%

TABLE 7
NP-59 Concentration in Euadrenal Tumors

Scintigraphic pattern in tumor (compared to contralateral gland)	No.
Increased	18
Decreased or distorted	9
Equal in both glands	8
Indeterminate	1
Helpful in defining tumor function:	27/36 or 75%.

patient alive and well four years later. The tumors larger than 5 cm included a myelolipoma, lymphoma, renal cell carcinoma, ganglioneuroma, adrenal cortical carcinoma and metastatic bronchogenic carcinoma.

Unilateral alteration of adrenal gland function could not be detected in the remaining nine cases; in seven of these cases the adrenal masses measured 1–4 cm on CT. NP-59 concentration was symmetric. There was subcutaneous extravasation of NP-59 in one case, and in another case two interpreters believed NP-59 concentration was symmetric, while the third believed concentration was decreased on the side opposite a 1.2-cm adrenal tumor. In only one of these nine cases was histologic correlation available (solitary cortical adenoma).

Residual Adrenal Glands. In this group of four cases, two patients had known malignancies. In the first case, a CT before right adrenalectomy for adrenal carcinoma demonstrated a small left adrenal nodule. Postoperatively, there was only left adrenal NP-59 concentration, consistent with surgery. In the second case, a left nephrectomy was performed 10 yr previously for renal cell carcinoma and more recently a lobectomy for adenocarcinoma of the lung. Subsequently, right adrenal enlargement was detected on CT and ultrasound. NP-59 concentration was only present on the right suggesting either previous left adrenalectomy during nephrectomy, a hyperfunctioning right adenoma suppressing the left adrenal, or less likely left adrenal destruction by disease as no mass in the adrenal bed was seen on CT. The patient was alive and well at follow-up 3 yr later. Another patient without biochemical abnormality exhibited bilateral asymmetrically enlarged adrenal glands on CT, with corresponding asymmetric but apparently normal NP-59 concentration (*27*). In the fourth case, NP-59 concentration was absent despite ACTH stimulation in a patient with Addison's disease studied to determine if there was any residual functioning adrenal cortical tissue.

Institutional Exchange

Of the 20 cases from the University of Michigan reviewed at Victoria Hospital, the six interpreters were in unanimous agreement in 19 cases (95%) regarding the sites of NP-59 uptake. In the single case of disagreement, five interpreters believed NP-59 concentration was bilateral and one unilateral. In one case with bilateral concentration, all six interpreters questioned the quality of the images and in another case the images were of such poor quality that the ability of all interpreters to confidently interpret them was impaired.

Of the 20 cases from Victoria Hospital, there was complete agreement in 17 cases. In one case, five of six interpreters believed the concentration was bilateral. In another case, four interpreters believed concentration was bilateral, one unilateral and one indeterminate due to image quality. In the third case, all three interpreters from Victoria Hospital agreed that concentration was bilateral, and the three interpreters from the University of Michigan believed it was unilateral; the reason for this remarkable discrepancy is unknown.

A high level of concurrence was found in 95% of the cases studied with unanimous agreement of all six interpreters in 36/40 cases (90%) and high agreement (5/6) in another two (95%). Of the cases meeting the diagnostic criteria for further evaluation at the University of Michigan, there was unanimous agreement by all three interpreters in 66/70 or 94% of the cases studied. In the remaining four cases, two of three interpreters agreed.

Safety

Eighty-five of 126 medical centers using NP-59 responded to the questionnaire. At the University of Michigan, 138 doses were given and a total of 729 doses were evaluated. Adverse reactions were reported for eight doses.

Seven minor reactions (self-limited reactions not requiring treatment) arose in six 2-mCi doses and in a 1-mCi dose. A 21-yr-old female with a history of adverse reactions to multiple procedures experienced the single intermediate reaction that required treatment. Nausea and dizziness developed at the end of a slow, 5-min, 2-mCi NP-59 injection. This was accompanied by flushing, headache, difficulty breathing, chest and back pain, a 10–20-sec loss of consciousness, tachycardia, and hypertension (150/110). After receiving 25 mg of diphenhydramine hydrochloride orally, her symptoms cleared within 1 hr and her vital signs stabilized. Other patients receiving injections from the same batch number experienced no adverse reactions. No patient had a severe, life-threatening reaction.

DISCUSSION

The accuracy for determining the site of excess hormone secretion by scintigraphy is high, ranging from 71% in the evaluation of primary aldosteronism to 100% in Cushing's syndrome, when the correct diagnostic criteria are met. This high level of accuracy in locating the site of hormone excess in Cushing's syndrome is of diagnostic value since the site of hormone production in this disorder may be unilateral or bilateral, and not always detected on CT (*19,28*). The most difficulty locating the site of hormone production was encountered in patients with primary aldosteronism. Given the small size of aldosterone producing adenomas and the availability of sensitive biochemical tests of the renin-angiotension-aldosterone axis, this was not unexpected. The percentage of correct diagnoses, 71%, is less than previously reported (*4,5,10,29–31*), perhaps, because the cases reviewed represented all stages of aldosteronism. Additionally, this may reflect changing referral patterns in which the most difficult and confusing cases are sent for scintigraphy.

Experience interpreting NP-59 scintigraphy in hyperandrogenism is limited (*11–14*) and cases were too few to draw a firm conclusion. Given good cross-sectional radiographic imaging and biochemical studies, other investigators have suggested NP-59 scintigraphy has potential in evaluating hyperandrogenism, and possibly in ovarian disorders, particularly when the site of excess hormone production is small, such as hyperthecosis and in functional, nontumorous abnormalities (*32*).

Scintigraphy successfully characterized 27 of 36 euadrenal tumors into functioning or nonfunctioning tumors. Unlike categories with hormonal disturbance, the indications for biopsy or excision in these cases was uncommon and histologic proof was frequently absent. NP-59 appears useful in distinguishing benign from malignant euadrenal tumors using the concept that functioning, NP-59 concentrating adrenal cortical tumors are benign, while nonfunctioning tumors are more worrisome and possibly malignant (*15*). Malignancy was common among the nine nonfunctioning tumors, particularly those >5 cm in diameter (100%). The nonfunctioning euadrenal tumors classified as benign were all <5 cm in diameter, supporting previous proposals that euadrenal tumors <5 cm in diameter on CT images can be treated as benign (*33,34*). While it is possible that functioning tumors larger than 5 cm will be found to be benign, and nonfunctioning tumors <5 cm will be malignant, this number will probably be few. Not infrequently, euadrenal tumors are associated with relative suppression of the contralateral adrenal gland function (*17*). NP-59 can provide useful information in such cases, because if the functioning tumor is removed, peri-operative corticosteroid replacement may be needed until function of the contralateral gland resumes.

In the final group of four assorted cases, help was requested for varying questions, but the small number makes it difficult to draw conclusions. Occasionally, surgeons must know if the adrenal glands remain when additional surgery near the adrenal bed is planned. NP-59 should be helpful in such cases, especially if previous surgical intervention or disease obscures anatomy on CT and MRI (*18*).

There appears to be little difficulty in reproducibly interpreting NP-59 scintigraphic images, when image quality is sufficient. Independent interpretations of NP-59 images at two different institutions showed remarkable levels of agreement.

Nevertheless, two particular pitfalls of NP-59 scintigraphy were recognized. These differ from the pitfalls that apply to nuclear medicine imaging in general such as subcutaneous injection of radiotracer. The greatest pitfall occurred when the clinical question was not clearly and fully stated. That is, when there was insufficient clinical and biochemical data to support a state of hormone excess, or in the case of euadrenal tumors, to exclude hormone excess. Similarly, if the clinical usefulness of NP-59 scintigraphy has not been established, as in the case of hyperandrogenism, particularly polycystic ovarian disease (*32*), then NP-59 scintigraphy could not be diagnostically efficacious. Concern for focused clinical questions led to the development of diagnostic criteria from standard texts (*21,22*) to guide the clinical question regarding the site(s) of excess cortisol, aldosterone or androgen production. The criteria for scintigraphy to evaluate euadrenal tumors are more easily defined as clear evidence of an adrenal tumor using radiographic images (CT, ultrasound, MRI) and the absence of excessive hormone secretion from both the adrenal cortex and medulla by clinical and biochemical data. Still, unless the hormonal status is clear, even the diagnosis of euadrenal tumor cannot be made with confidence.

In 23 patients undergoing NP-59 scintigraphy in this study, the clinical question was improper and no diagnostic interpretation of images was possible. For example, in cases referred for the evaluation of euadrenal tumors, if there was insufficient clinical data to support or exclude the diagnosis of Cushing's syndrome (*21, 22*), the scintigraphic pattern of unilateral left adrenal activity could be interpreted as either a Cushing's adenoma (Fig. 1) or euadrenal tumor (Fig. 2). Therefore, clinical and biochemical information are essential to proper interpretation. In the majority of cases referred for the evaluation of hyperandrogenism, 8 of 10 had testosterone levels <1.8 ng/dl. Each was thought to

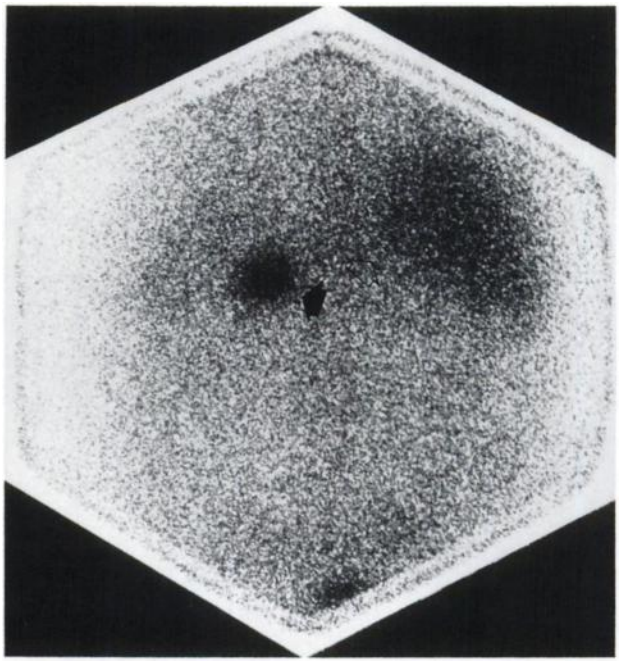

FIGURE 1
Unilateral intense NP-59 concentration in the left adrenal gland with suppression of contralateral adrenal gland uptake in a left adrenal Cushing's adenoma; image on day 5 after injection of NP-59.

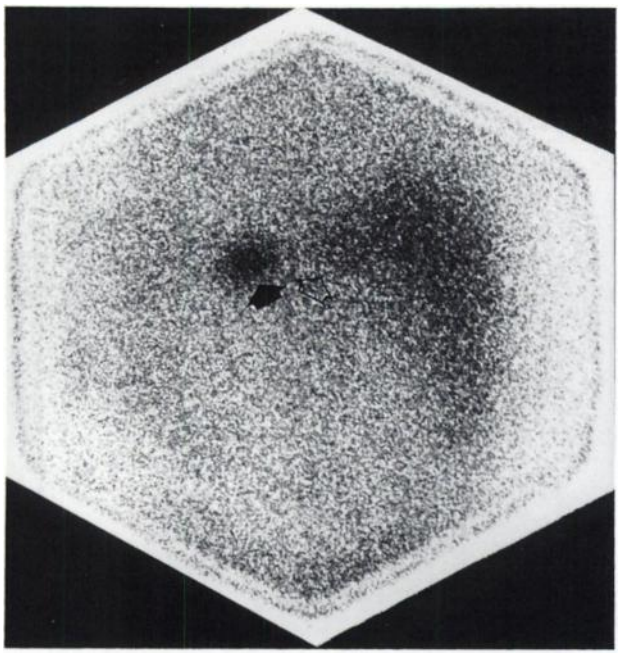

FIGURE 2
Functioning left euadrenal tumor in a patient without detectable clinical or biochemical evidence of hormone hypersecretion; there is little difference in the appearance of this image from Figure 1.

have a functional disorder such as polycystic ovarian disease, a diagnosis made with clinical and biochemical data.

The second pitfall of NP-59 scintigraphy was the patient preparation prior to the study. In the evaluation of all patients, the major steps in preparation include a laxative to reduce NP-59 activity in the colon (*35*), the injection of the correct radiotracer dose, and the scheduling of images over a sufficient number of days to obtain adequate images of the adrenal glands. When imaging for primary aldosteronism, images must be scheduled to observe the earliest appearance of adrenal radioactivity (*5*), as early unilateral concentration suggests the presence of a functioning adrenal adenoma. In addition, it is essential that dexamethasone be given for a week prior to injection and during imaging to reduce the function of the normal cortisol-producing adrenal cortical tissue.

NP-59 scintigraphy is a useful modality to functionally characterize adrenal abnormalities detected with cross-sectional radiographic imaging and is useful to determine the functional (benign) or nonfunctional (potentially malignant) nature of adrenal masses detected incidentally. While CT and MRI have comparable sensitivities in detecting lesions >1–1.5 cm, CT may be superior to MRI in detecting lesions <1 cm. While this may improve with the application of newer technology, given this and the inability of MRI to characterize adrenal function, CT is perhaps a better study for delineation of morphologic abnormalities, especially for the detection of aldosteronomas (usually <1 cm) and nodular hyperplasia, and less for Cushing's adenomas (usually >2 cm) (*28*). Beyond this, NP-59 scintigraphy can detect functional abnormalities below the spatial resolution of CT and MRI, especially tiny aldosteronomas or functional hyperplasia in normal-sized adrenal glands, and therefore has an important role in the evaluation of adrenal cortical abnormality.

CONCLUSIONS

In any procedure, care must be taken, but especially with NP-59 scintigraphy, interpretation is dependent on the formulation of the proper clinical question based on thorough clinical and biochemical evaluation. Given adequate clinical, biochemical, and radiographic information; reproducible image interpretation; and the safety of [iodine-131]6-beta-iodomethyl-19-norcholesterol, NP-59 scintigraphy is an excellent modality for determining the site(s) and nature of adrenal cortical and perhaps ovarian abnormalities.

ACKNOWLEDGMENTS

This research was directly supported by FDA grant #FD-R-000130 and by a previous CRC grant.

The authors thank Karen Grahl for her expert assistance in the preparation of this manuscript and the many physicians who referred their patients for evaluation. Additional thanks to T. Mangner, PhD and the Phoenix Memorial Laboratory for the synthesis of NP-59 and the use of their radiochemical facilities.

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