The Relationship of Serum Lipids to Adrenal-Gland Uptake of 6β-[^{131}I] Iodomethyl-19-Norcholesterol in Cushing's Syndrome

Timothy W. Valk, Milton D. Gross, John E. Freitas, Dennis P. Swanson, David E. Schteingart, and William H. Beierwaltes

The University of Michigan Medical Center Ann Arbor, Michigan

An alteration in serum cholesterol levels has been suggested as a possible modifier of adrenal uptake of the cholesterol analog, 6β-[^{131}I]iodomethyl-19-norcholesterol (NP-59). To assess the effect of hypercholesterolemia upon NP-59 adrenal uptake, patients with Cushing's syndrome (eight with pituitary-dependent, four with ACTH-independent, and two with ectopic-ACTH syndrome) were selected for retrospective analysis based on the availability of serum cholesterol (n = 14) and triglyceride (n = 10) concentrations obtained at the time of adrenal scintigraphy. A negative correlation ($r = -0.78$, $p < 0.01$) was found between NP-59 uptake and serum cholesterol levels in patients with pituitary-dependent Cushing's disease. Compared with pituitary-dependent disease, the ectopic-ACTH syndrome and ACTH-independent states demonstrated equal or greater adrenal uptake of NP-59 at similar serum cholesterol concentrations. Serum triglyceride concentrations did not correlate with total adrenal uptake of NP-59 in any of the patient groups studied.

Increased serum cholesterol concentrations are associated with diminished adrenal uptake of NP-59, and in some cases may limit the diagnostic efficacy of adrenal scintigraphy in Cushing's syndrome.

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Adrenal scintigraphy using 6β-[^{131}I]iodomethyl-19-norcholesterol (NP-59) has become a useful technique for locating adrenal cortical abnormalities in patients with Cushing's syndrome. Following NP-59 administration, the patterns of adrenal visualization in this disease state are: (a) unilateral uptake compatible with an adrenal adenoma; (b) bilateral symmetrical increased uptake suggestive of ACTH-dependent disease or the asymmetrical bilateral uptake of autonomous bilateral hyperplasia; and (c) bilateral nonvisualization from adrenal carcinoma (*1,2*). Therefore the correct diagnosis of adrenal disease using NP-59 scintigraphy is dependent upon quantification of adrenal uptake, but biological factors that may alter uptake of NP-59 have not been well defined.

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For reprints contact: Timothy W. Valk, MD, Div. of Nuclear Medicine, Univ. of Michigan Medical Ctr., Ann Arbor, MI 48109.

Although the adrenal gland is capable of synthesizing cholesterol *de novo* (*3,4*), over 80% of this substrate for adrenal steroidogenesis is derived from low-density lipoproteins (LDL) receptor transport of serum cholesterol into the adrenal cortex (*5,6*). Since NP-59 is a cholesterol analog, it is assumed that it shares with native cholesterol the mechanisms that transport it into the gland (*7*). Hence, conditions that produce hypercholesterolemia (such as Cushing's syndrome) (*8*) might be expected to modify the uptake of NP-59 into the adrenal gland as a result of dilution in the enlarged serum cholesterol pool, or a reduction in the number or affinity of adrenal LDL-cholesterol receptor sites. The effect of this modification, an apparently lower adrenal uptake of NP-59, may limit the diagnostic efficacy of adrenal scintigraphy in Cushing's syndrome. In view of a recent case report (*9*) suggestive of this phenomenon, we undertook a retrospective analysis to determine the relationship between NP-59 adrenal gland uptake and serum

cholesterol and triglyceride levels in Cushing's syndrome.

METHODS

Fourteen patients, eight with pituitary dependent Cushing's disease, four with ACTH-independent disease (either adrenal adenoma or bilateral nodular hyperplasia), and two with ectopic-ACTH syndrome were selected for retrospective analysis based on the availability of concomitant serum lipid measurements obtained at the time of initial adrenal scintigraphy in the investigation of Cushing's syndrome. Serum cholesterol and triglyceride concentrations were determined by cholesterol oxidase in 14 patients and by Hantzch fluorometry in ten. During the study period, none of the patients received adrenolytic or other agents that suppress steroidogenesis, nor did they receive drugs known to alter serum cholesterol or triglyceride levels.

Adrenal scintigraphy was performed as previously described. Patients were given Lugol's solution, three drops twice daily, the day before and 7 days after injection of NP-59.* The radiocholesterol dose is 1 mCi/1.7 m^2 of body area, administered i.v. over 1-2 min; and specific activity ranges 1-5 mCi/mg cholesterol. Imaging was performed 3, 4, and 5 days after injection. A standard gamma camera was used, with higher-energy, parallel-hole collimator, to obtain posterior and lateral projections. An 80-keV window centered at 364 keV is used and patients are imaged for 20 min or a minimum of 50,000 counts.

The adrenal uptake as percent adminstered dose of NP-59 was calculated using a semi-operator-independent computer algorithm (*10*). The operator supplies the coordinates of a point in the center of each adrenal by inspection of the computer display. The algorithm then flags all surrounding points corresponding to the adrenal. The adrenal background is determined from a strip of data cells immediately surrounding each adrenal, and calculation of the net counts for each adrenal follows directly. The net count is then related to a standard percent-uptake dose curve obtained from phantom studies. Individual left- and right-gland uptakes were summed and results expressed as total percent administered dose uptake of NP-59. Coefficients of correlation were determined comparing serum cholesterol and triglyceride levels with the percent total adrenal uptake of NP-59. Statistical significance was determined using Student's t-tests.

RESULTS

Serum cholesterol and triglyceride concentrations ranged between 145-390 mg/dl and 75-326 mg/dl, respectively. Total adrenal uptake of NP-59 varied from 0.23 to 2.02% of the administered dose. Higher NP-59 adrenal uptakes ($p < 0.05$) were found in the ACTH-independent and ectopic-ACTH groups than in patients with pituitary-dependent Cushing's disease (Table 1).

TABLE 1. TOTAL ADRENAL UPTAKE OF NP-59 IN CUSHING'S SYNDROME*

ACTH-independent and ectopic-ACTH (n = 6)	1.23 ± 0.25%†
Pituitary-dependent (n = 8)	0.50 ± 0.09%
Normal subjects (n = 15)	0.33 ± 0.07%

* % Dose administered (right + left).

† Mean ± s.e.m. $p < 0.05$ as compared with pituitary-dependent.

Relationship between serum cholesterol concentration and total adrenal uptake of NP-59. A negative correlation ($r = -0.78$, $p < 0.01$) was observed between serum cholesterol concentrations and adrenal uptake of NP-59 in the eight patients with pituitary-dependent Cushing's disease (Fig. 1). Patients with ACTH-independent and

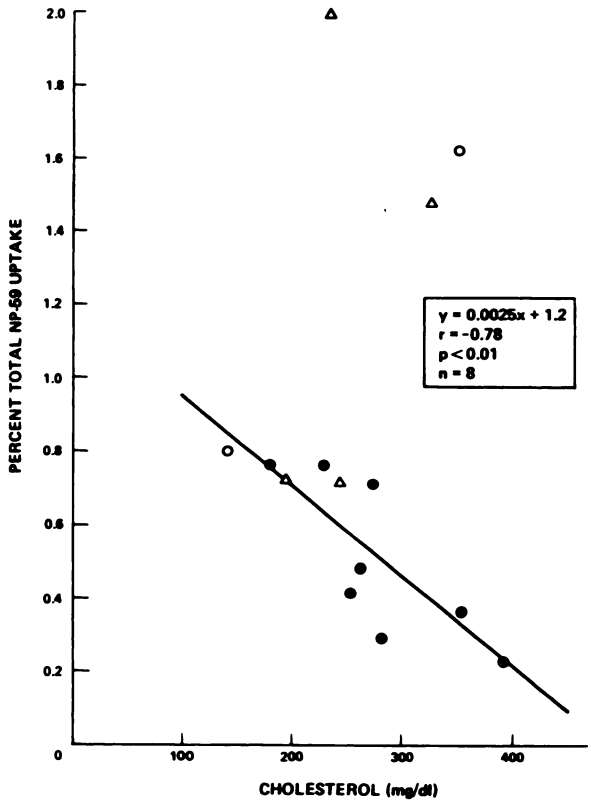

FIG. 1. Relationship of adrenal uptake of NP-59 and serum cholesterol concentrations in pituitary-dependent (●), ACTH-independent (△), and ectopic-ACTH (○) syndromes. Linear regression equation for pituitary-dependent Cushing's syndrome is shown.

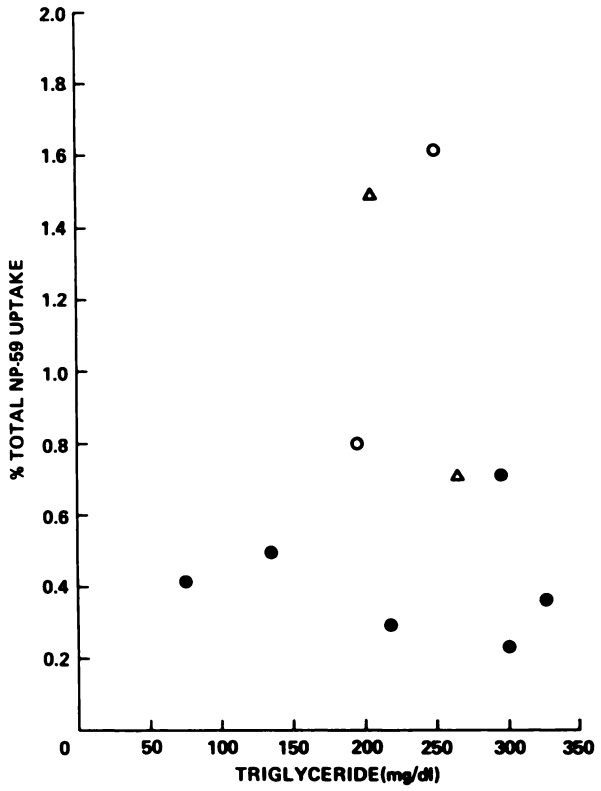

FIG. 2. Relationship of adrenal uptake of NP-59 and serum triglyceride concentrations (same symbols as in Fig. 1).

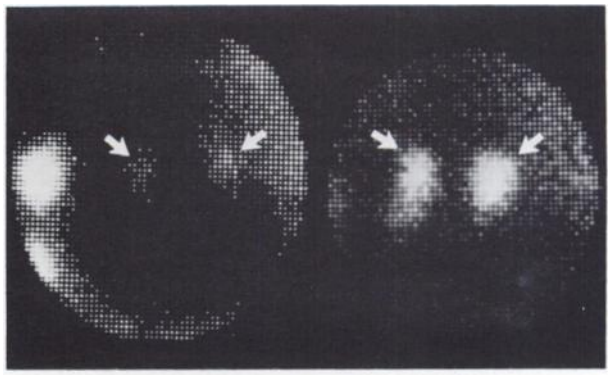

FIG. 3. Posterior adrenal scintigrams on Day 5 (with 10% background subtraction) in two patients with Cushing's disease. Patient at left had serum cholesterol 390 mg/dl, total adrenal NP-59 uptake of 0.23% (normal 0.33 ± 0.07%) (*1*), and urinary free cortisol 1159 μg/day (normal 30–150 μg/day). Patient at right had serum cholesterol of 200 mg/dl, NP-59 uptake of 0.78%, and urinary free cortisol 1950 μg/day. Arrows indicate adrenals, with liver activity overlying right adrenal and bowel activity below left adrenal.

ectopic-ACTH syndromes behaved in a variable manner. At similar cholesterol concentrations, three of these patient's demonstrated adrenal uptakes of NP-59 that were equivalent, and the remaining three patients exhibited uptakes that were greater than in patients with pituitary-dependent Cushing's disease.

Relationship between serum triglyceride concentrations and total adrenal uptake of NP-59. There was no demonstrable correlation of serum triglyceride levels with NP-59 uptake in patients with pituitary-dependent, ACTH-independent, or the ectopic-ACTH syndrome in the patients studied (Fig. 2).

DISCUSSION

The control of adrenal cholesterol uptake is dependent upon: (a) the prevailing pituitary adrenocorticotropin (ACTH) levels, (b) the intra- and extracellular adrenal cholesterol levels, (c) the availability of low-density lipoproteins (LDL) for transport of cholesterol to the adrenocortical sites of absorption, and (d) the number and the affinity of the adrenocortical LDL-membrane-bound receptors (*3–6,11–13*). Since the control of cholesterol uptake is affected by these factors, it also appears that uptake of NP-59 is so affected. Gordon et al. (*9*) have reported the absence of adrenocortical visualization using NP-59 in a patient with Cushing's syndrome who had marked hypercholesterolemia and hyperlipoproteinemia. The present series confirms the effect of an expanded cholesterol pool upon the uptake of NP-59 in Cushing's syndrome, since there is a significant negative correlation between calculated NP-59 uptake and serum cholesterol concentrations in patients with Cushing's disease. An attractive explanation for this phenomenon would be a dilutional effect upon radiotracer concentrations, but speculation as to the possible role of LDL-receptor affinity or number cannot be determined from the present investigation.

It is intriguing that patients with nonpituitary ectopic-ACTH syndrome, unilateral adenoma, or bilateral nodular hyperplasia exhibit adrenocortical NP-59 uptakes that are elevated as compared with patients with pituitary-dependent Cushing's disease at similar cholesterol levels. The greater plasma ACTH levels in patients with ectopic-ACTH syndrome (900–1000 pg/ml) than in patients with pituitary-dependent Cushing's disease (72–240 pg/ml) might diminish the effect of the cholesterol pool upon iodocholesterol uptake. In patients with intrinsic adrenocortical disease, a loss of the normal mechanisms of controlling uptake would account for the variable effect of the cholesterol pool on autonomously functioning tissues.

The inverse relationship between cholesterol and NP-59 uptake suggests that patients with serum cholesterol levels above 400–500 mg/dl may not provide adequate iodocholesterol uptake for imaging. Patients with serum cholesterol levels of 300–400 mg/dl demonstrate poor adrenal cholesterol iodocholesterol visualization (Fig. 3), similar to normal subjects (*1*). Target-to-nontarget ratios are decreased, and interpretation of such studies is more difficult.

Therefore, the correct interpretation of the adrenocortical scintigram should be based upon a knowledge

of the pathologic processes under study, the conditions under which the scan is performed, and the endogenous cholesterol pool. When suboptimal iodocholesterol uptake is observed in cases of Cushing's syndrome, and other technical factors can be excluded, hypercholesterolemia should be considered as a causative factor.

FOOTNOTE

* NP-59 was obtained from the Nuclear Pharmacy, Div. of Nuclear Medicine, University Hospital, Ann Arbor, MI 48109.

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