The Normal Dexamethasone-Suppression Adrenal Scintiscan

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To establish the parameters of adrenal imaging under dexamethasone suppression (DS), 18 normotensive, normal male volunteers underwent dexamethasone-suppression adrenal scintiscanning. Five control groups were established and given dexamethasone, either 8 mg for 2 days or 4 mg for 7 days before 6β-[^{131}I] iodomethyl-norcholesterol (NP-59) administration. NP-59 was given in doses of 2, 1, or 0.5 mCi. Early visualization (3–5 days) of the adrenals was noted in the groups on the 8 mg DS regimen with either 1 or 2 mCi of NP-59. Late visualization (5–7 days) was noted in the groups that received 4 mg DS and either 2, 1, or 0.5 mCi of NP-59, respectively. The normal adrenal will demonstrate uptake of NP-59 under DS, and the duration of DS before imaging is the critical factor as to when discernible adrenal visualization will occur. The documentation of the normal suppression interval on these DS regimens provides a basis for the correct diagnostic interpretation of adrenal hyperfunction as seen on the dexamethasone-suppression NP-59 adrenal scan.

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The suppression of pituitary adrenocorticotropin (ACTH) with dexamethasone (DS) has been shown to enhance the sensitivity and diagnostic accuracy of adrenal scintigraphy in detecting aldosteronomas and distinguishing them from bilateral adrenal hyperplasia (*1–5*). With 6β-[^{131}I] iodomethyl-norcholesterol (NP-59) we have demonstrated that DS adrenal scintigraphy correctly detected adenomas in 90% of cases and also distinguished hyperplasia from adenoma in 90% of cases (*4*). Initial studies with 19-[^{131}I] iodocholesterol (NM-145) demonstrated late but discernible imaging (breakthrough) of the contralateral adrenal gland in patients with aldosterone-producing adenomas (*1–3*). This breakthrough of iodocholesterol uptake under DS was accentuated with the introduction of NP-59 due to the marked increase of adrenal cortical uptake seen with this agent (*5, 6*). Under DS using NP-59, the contralateral adrenal gland in patients with aldosteronomas visualized earlier than glands observed with NM-145 (*3–5*). This phenomenon makes the diagnostic interpretation of DS adrenal scintigrams more difficult especially in those cases in which distinction of aldosteronoma from hyperplasia cannot be made by other noninvasive means.

The present investigation was undertaken to answer the following questions: (a) does variation of the dose or duration of dexamethasone administration alter normal adrenal gland visualization time (time interval from tracer injection to successful adrenal gland imaging); (b) does variation in the amount of NP-59 activity administered alter this visualization time; and (c) what is the optimal tracer dose and suppression regimen for DS adrenal imaging?

METHODS

Informed consent was obtained from 18 normotensive, male volunteers, ages 25–30 yr, who were divided into five groups (I–V, Table 1). Group I (n = 3) received 8 mg of dexamethasone daily in divided doses, starting 48 hr before i.v. administration of 2 mCi of NP-59* and continued throughout the duration of the study. Group II (n = 3) received the same dexamethasone regimen,

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TABLE 1. DEXAMETHASONE-SUPPRESSION ADRENAL IMAGING

Group	DS* (mg/d)	NP-59 (mCi)	First day of visualization	Cortisol (μg/dl)	17-OH (mg/d)	17-KS (mg/d)
I	8/2	2	3	—	—	—
	8/2	2	5	—	—	—
	8/2	2	3	0.45	1.3	4.7
II	8/2	1	4	0.93	1.5	6.5
	8/2	1	3	0.28	1.9	7.8
	8/2	1	4	1.49	5.1	12.1
III	4/7	2	5	—	—	—
	4/7	2	6	0.47	1.1	8.0
	4/7	2	7	0.09	1.7	6.8
IV	4/7	1	none†	0.18	0.9	4.7
	4/7	1	5	0.40	2.3	7.4
	4/7	1	7	1.00	0.9	7.0
	4/7	1	6	0.40	1.1	4.2
	4/7	1	none†	0.93	1.0	10.7
	4/7	1	5	0.40	1.2	7.8
V	4/7	0.5	5	0.40	1.8	6.5
	4/7	0.5	6	0.48	1.0	3.8
	4/7	0.5	5	0.40	1.9	7.2

* DS given in divided doses; 8/2 = 8-mg DS started 2 days before injection and continued throughout imaging interval. 4/7 = 4-mg DS started 7 days before injection and continued throughout imaging interval.

† Imaged 2 days later after DS was stopped.

but only 1 mCi of NP-59. Three groups (III, IV, and V) received 4 mg of dexamethasone daily in divided doses for 7 days before radiotracer administration and continued throughout the imaging sequence. NP-59 was administered intravenously in 2 mCi (III, n = 3), 1 mCi (IV, n = 6), or 500 μCi (V, n = 3) doses. To suppress thyroidal uptake of free I-131, all volunteers received Lugol's iodine, three drops twice daily, beginning 48 hr before NP-59 administration and continuing throughout the imaging sequence. The NP-59 was prepared as previously described (*4*). Posterior adrenal imaging was performed at 72, 96, and 120 hr after NP-59 administration using a standard gamma camera (high-energy, parallel-hole collimator) interfaced to a minicomputer. Images were obtained at later time intervals in cases in which there was no adrenal visualization at the 120-hr interval. Both analog and computer-enhanced digital images were recorded on Polaroid film. Scintigrams were interpreted as "adrenal gland visualization" when two observers detected adrenal gland uptake on two successive days. Adrenal uptakes were calculated using the method of Koral and Sarkar (*7*).

To assess the adequacy of adrenal suppression, 24-hr urine collections were obtained for 17-hydroxysteroids (17-OH) and 17-ketosteroids (17-KS) 1 day before imaging. On the first day of successful adrenal visual-

TABLE 2. DEXAMETHASONE SUPPRESSION OF NP-59 UPTAKE

Dexamethasone (mg)	8	4
Number of controls	6	12
Suppression interval (days)	3.7 ± 0.45*,†	5.9 ± 0.41
Mean cortisol (μg/dl) (normal 10–20 μg/dl)	0.47 ± 0.29‡	0.43 ± 0.06
Mean 17-OH (mg/24 hr) (normal 5–10 μg/24°)	1.35 ± 0.29‡	1.24 ± 0.20
Mean 17-KS (mg/24 hr) (normal 6–20 μg/24°)	7.7 ± 1.48‡	6.73 ± 0.37

* Expressed as mean ± s.e.m.

† $p < 0.01$ by Student's t-test (8-mg compared with 4-mg regimen).

‡ Not significant (8-mg vs. 4-mg regimen).

ization, a plasma cortisol was obtained.

RESULTS

Both DS regimens achieved comparable degrees of adrenocortical hormone suppression, as demonstrated in Table 1. The mean plasma cortisols and urinary 17-hydroxysteroids in all groups were identical and there were no significant differences in mean urinary 17-ketosteroid excretion under dexamethasone suppression (Table 2).

In the two groups that received the 8-mg DS regimen and either 1 or 2 mCi of NP-59, the suppression intervals and images were comparable (Figs. 1A and B). Groups III, IV, and V, which received the 4-mg DS regimen, provided imaging that was later than in Groups I and II, irrespective of the dose of NP-59. In two individuals (Group IV) there was no adrenal uptake of NP-59 after a 7-day imaging interval. Cessation of dexamethasone administration resulted in imaging 2 days later (Figs. 2A and B). The mean imaging time in Groups I and II was 3.7 days, and in Groups III, IV, and V it was 5.9 days (Table 2).

All controls were able to complete the DS regimens without difficulty. DS was given for 12 to 14 days in the 4-mg subjects (Groups III–V) and 7 to 9 days in the 8-mg subjects (I and II). There were no significant side effects from either DS or Lugol's iodine. Minor complaints were insomnia, euphoria, and hyperphagia.

The quality of the adrenal images obtained under dexamethasone suppression was lower than in those under nonsuppression conditions. Decreased adrenal uptake of tracer and higher background activity resulted in lower target-to-background ratios than were encountered in nonsuppressed individuals. In the test cases, uptake calculations were adversely affected as a result of this low target-to-background ratio. Relatively higher liver and bowel activity made identification and resolution of the adrenal glands difficult in some instances (Figs. 3A and B).

DISCUSSION

The application of dexamethasone suppression to adrenal scintigraphy has provided an alternative approach to the evaluation of patients with primary aldo-

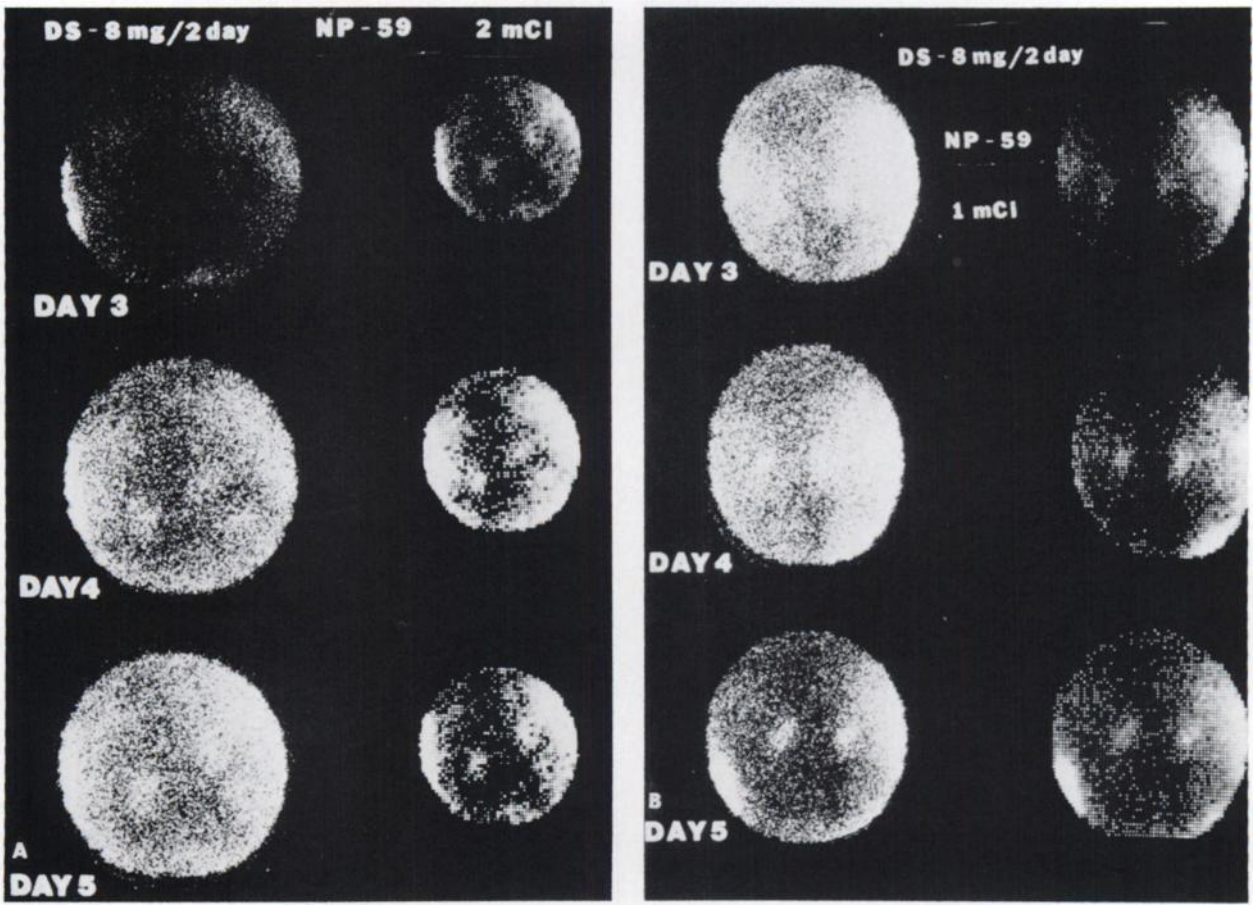

FIG. 1. (A) Posterior analog (left) and computer-enhanced (right) adrenal images on Days 3, 4, and 5 after 2 mCi NP-59. Normal subject, prepared with 8 mg dexamethasone on each of 2 days before NP-59.
(B) Posterior analog (left) and computer-enhanced (right) adrenal images on Days 3, 4, and 5 after 1 mCi NP-59. Normal subject, prepared with 8 mg dexamethasone on each of 2 days before NP-59.

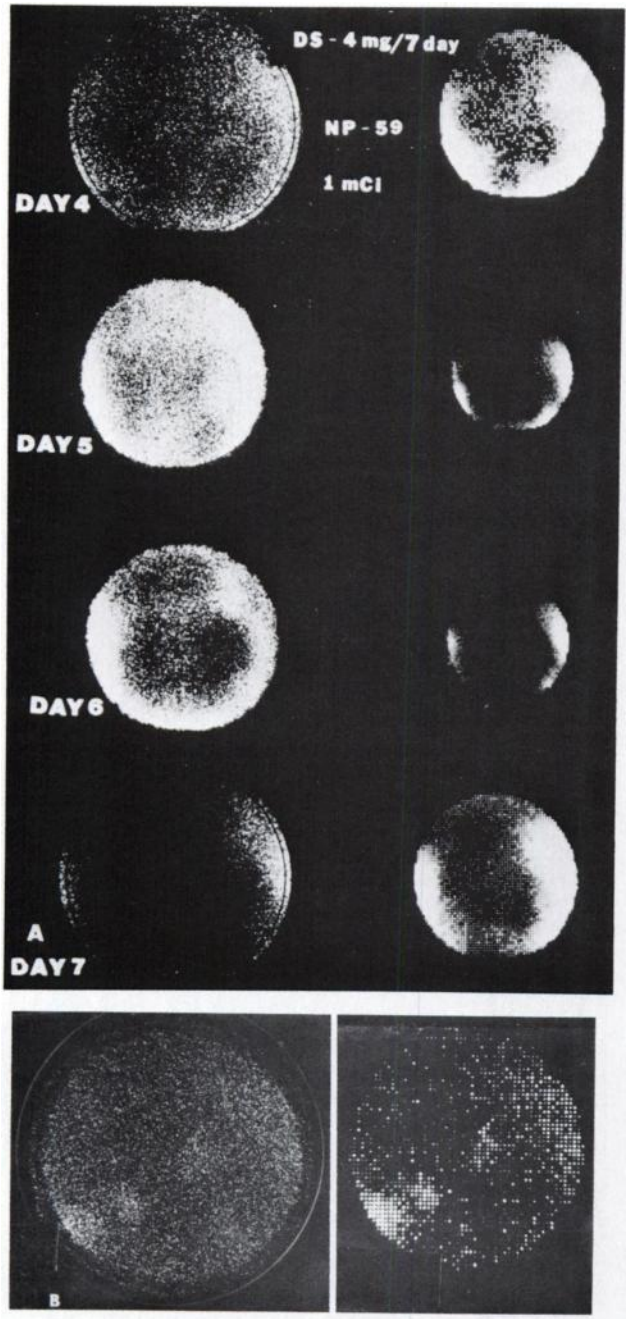

FIG. 2. (A) Posterior analog (left) and computer-enhanced (right) adrenal images on Days 4, 5, 6, and 7 after 1 mCi NP-59. Normal subject, prepared with 4 mg dexamethasone on each of 7 days before NP-59. Note no visible adrenal activity.
(B) Posterior analog (left) and computer-enhanced (right) adrenal images of normal subject 2 days after dexamethasone (4 mg/day for 7 days) was discontinued. Note presence of bilateral adrenal activity.

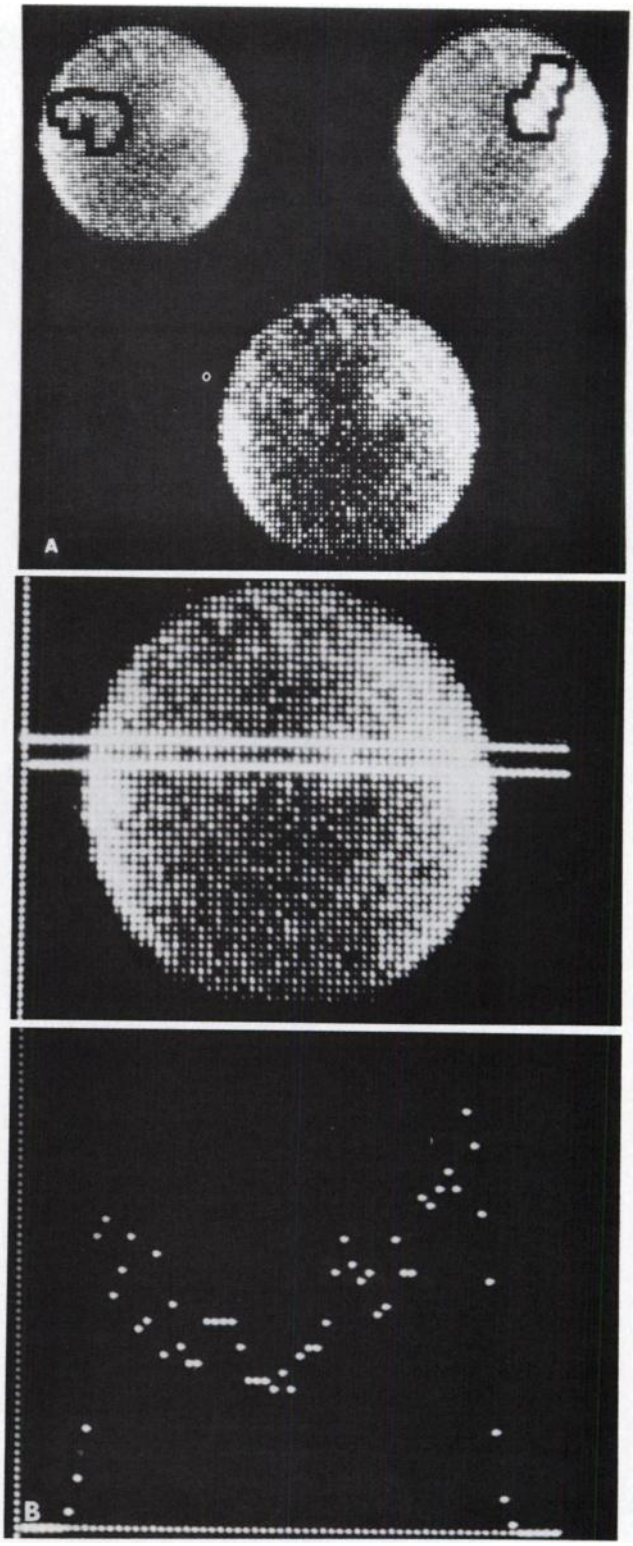

FIG. 3. (A) Posterior adrenal images of normal subject prepared with dexamethasone (4 mg/day for 7 days) before 1 mCi NP-59 at the 5-day interval. Note high background activity and failure of computer's edge-detection program to define area of adrenal uptake.
(B) Activity profile of adrenal scintigram of normal subject prepared with dexamethasone (4 mg/day for 7 days) before 1 mCi NP-59 at the 5-day interval. Note low target-to-background ratio.

steronism. Earlier reports have noted the presence of adrenal uptake of either NP-59 or NM-145 at intervals that would not be expected in normal glands under DS. Seabold et al. (*1*) and Conn et al. (*2*), using NM = 145, noted progressively increasing activity in the contralateral adrenal gland resulting in visualization within the

5-day interval after tracer administration. Sarkar et al. (*5*) noted NP-59 uptake in the unaffected adrenals of DS patients with aldosteronomas. As the duration and the dose of dexamethasone was increased, this uptake was decreased and delayed. Normals were not included in these initial studies.

The results of this investigation indicate that the normal adrenal will concentrate NP-59 under dexamethasone suppression. In spite of maximal suppression of plasma cortisol and urinary 17-hydroxysteroids, measurable uptake of NP-59 is evident at variable intervals after radiotracer administration. Although ACTH was not measured in this study, Conn et al. (*2*) previously reported ACTH suppression under these conditions. The duration of DS dosage before NP-59 administration appears to be the important factor in the delayed appearance of adrenal gland visualization. In cases of aldosteronoma, continuous DS results in transient early decreases of plasma aldosterone levels, which have been observed to return to near baseline at 72 hr in spite of significant suppression of plasma cortisol at the corresponding intervals (*8*). Consistent dexamethasone suppression of plasma aldosterone has not been observed in either normals or cases of bilateral adrenal hyperplasia resulting in primary aldosteronism (*9, 10*). These observations may explain the occurrence of false-negative scan results, particularly in those cases involving small aldosteronomas with brief dexamethasone-suppression schemes.

The mechanism of breakthrough of NP-59 uptake under DS is currently unknown. Levels of urinary 17-hydroxysteroids and plasma cortisol indicate adequate suppression of basal adrenal steroid production. Clearly mechanisms other than ACTH-mediated adrenal-gland tracer uptake are operative under DS. The intra- and extracellular adrenal cholesterol pool and serum lipoproteins may have considerable bearing upon NP-59 uptake (*11, 12*). Although the present study does not propose to answer these questions, it is apparent that adrenal uptake of radiocholesterol (NP-59) under DS can be dissociated from adrenal steroid production and/or release in normal subjects.

The diagnostic implications of normal adrenal visualization of NP-59 under DS are critical. Dexamethasone, at doses of 8 mg for 2 days or 4 mg for 7 days before NP-59 administration, will result in minimal adrenal visualization after 3 or 5 days, respectively. Uptake before that time, either unilateral or bilateral, is considered to be abnormal and indicative of adrenal adenoma or hyperplasia in cases of primary aldosteronism (*4–6*). Additional studies are in progress to explore the mechanism and significance of breakthrough of NP-59 adrenal uptake under dexamethasone suppression.

FOOTNOTE

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

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