Use of low- and high-dose dexamethasone tests for distinguishing pituitary-dependent from adrenal tumor hyperadrenocorticism in dogs

Edward C. Feldman, DVM; Richard W. Nelson, DVM; Marsha S. Feldman, BS

Objective—To evaluate low- and high-dose dexamethasone suppression tests for differentiating pituitary dependent hyperadrenocorticism (PDH) from adrenal tumor hyperadrenocorticism (ATH) in dogs.

Design—Prospective study.

Animals—181 dogs with PDH and 35 dogs with ATH.

Procedure—Plasma cortisol concentrations from dogs with naturally developing hyperadrenocorticism were evaluated before, and 4 and 8 hours after administration of standard low- and high-doses of dexamethasone (0.01 mg/kg of body weight, IV, and 0.1 mg/kg, IV; respectively).

Results—In response to the low-dose test, all but 3 dogs had an 8-hour post-dexamethasone plasma cortisol concentration that was consistent with a diagnosis of hyperadrenocorticism, that is, ≥ 1.4 µg/dl. Criteria used to distinguish PDH from ATH in response to low-dose dexamethasone included a 4-hour post-dexamethasone plasma cortisol concentration < 50% of the basal value or < 1.4 µg/dl, or an 8-hour post-dexamethasone plasma cortisol concentration < 50% of the basal concentration. Criteria used to distinguish PDH from ATH in response to high-dose dexamethasone included 4- or 8-hour post-dexamethasone plasma cortisol concentrations < 50% of the basal concentration or < 1.4 µg/dl. In response to the low-dose test, 111 dogs met criteria for suppression (each had PDH). In response to the high-dose test, 137 dogs met criteria for suppression (2 had ATH, 135 had PDH). Twenty-six dogs with PDH (12%) had indications of adrenal suppression in response to high-dose but not low-dose testing.

Clinical Implications—Low-dose dexamethasone test has value as a discrimination test to distinguish dogs with PDH from those with ATH. The high-dose test need only be considered in dogs with hyperadrenocorticism that do not have adrenal suppression in response to the low-dose test. (*J Am Vet Med Assoc* 1996;209:772–775)

Naturally developing hyperadrenocorticism in dogs is a well-recognized and common disorder. Approximately 10 to 20% of dogs with hyperadrenocorticism have an autonomously functioning adrenocortical adenoma or carcinoma (adrenocortical tumor hyperadrenocorticism [ATH]).[1-3] Most dogs with hyperadrenocorticism have bilateral adrenocortical hyperplasia as a result of chronic excessive adrenocorticotropic hormone (ACTH) secretion by the pituitary gland (pituitary-dependent hyperadrenocorticism [PDH]).[4,5]

Several endocrine tests have been developed that aid in screening for hyperadrenocorticism (ie, they help separate dogs that have naturally developing hyperadrenocorticism from those that do not). Among the most commonly recommended screening tests are the ACTH stimulation test, the low-dose dexamethasone test, and the urine cortisol/creatinine ratio.[6-10] Because the treatment, long-term complications, and prognosis are dependent, in part, on the cause of the disorder, additional tests are recommended to aid in discriminating dogs with PDH from those with ATH. Included among these discrimination tests are abdominal radiography and ultrasonography, determination of endogenous plasma ACTH concentrations, high-dose dexamethasone tests, and, more recently, computed tomography (CT) or magnetic resonance imaging (MRI) of the brain.[7,11-18]

It has been suggested that results of the low-dose dexamethasone test be used to help discriminate between PDH and ATH in dogs.[19,20] The purpose of the study reported here was to evaluate results of the low-dose dexamethasone test in dogs as a tool for discriminating PDH from ATH, and to evaluate the need for high-dose dexamethasone testing in dogs initially evaluated with the low-dose test.

Materials and Methods

Dogs—This prospective study was completed with dogs evaluated at our teaching hospital between Jan 1, 1990 and Mar 1, 1995. To be included in this study, each dog must have been suspected to have hyperadrenocorticism on the basis of history and the results of physical examination, CBC, serum biochemical analysis, and urinalysis. Dogs could not have any notable disorder involving other organ systems. The diagnosis of hyperadrenocorticism must have been confirmed with abnormal results on at least 2 of the following 3 screening tests: ACTH[a] stimulation (post-ACTH plasma cortisol concentration > 17 µg/dl), low-dose dexamethasone (8-hour post-dexamethasone plasma cortisol concentration ≥ 1.4 µg/dl), and urine cortisol/creatinine ratio ($> 1.35 \times 10^{-5}$).[6,10]

Dogs with a diagnosis of ATH must have had an endogenous plasma ACTH concentration < 10 pg/ml and had 1 mass identified in the area of 1 adrenal on abdominal ultrasonography.[7,12] Additional adrenal tissue could not have been identified in either adrenal area via ultrasonography. Further, these dogs must have had an adrenocortical tumor (adenoma or carcinoma) identified on histologic examination of tissue removed during celiotomy or at necropsy.

Dogs with a diagnosis of PDH must have had an endogenous plasma ACTH concentration ≥ 50 pg/ml and each must have had 2 relatively equal-sized adrenal glands identified by use of abdominal ultrasonography.[7,12] Each of these dogs must have been treated with the adrenocorticolytic drug mitotane and each must have had good response to therapy within 30 days, or had a pituitary mass identified on CT or

From the Department of Medicine and the Veterinary Medical Teaching Hospital, University of California, Davis, CA 95616.

Supported in part by the Companion Animal Laboratory, School of Veterinary Medicine, University of California, Davis, and by a contribution from Ms. Ruth Johnston, San Mateo, Calif.

MRI scans, or have had evidence of bilateral adrenocortical hyperplasia at necropsy.

Dexamethasone tests and interpretation—To be included in this study, each dog must have had blood samples collected before, and 4 and 8 hours after, IV administration of 0.01 mg of dexamethasone/kg of body weight (low-dose test). This test was begun between 7:45 and 9:00 AM on a day when other testing of any kind was not performed. An 8-hour post-dexamethasone plasma cortisol concentration ≥ 1.4 µg/dl was considered consistent with (screening for) a diagnosis of hyperadrenocorticism. Without interfering with the results of the low-dose screening test, 3 additional criteria were used to discriminate PDH from ATH. These 3 criteria included: (1) a 4-hour post-dexamethasone plasma cortisol concentration < 1.4 µg/dl; (2) a 4-hour post-dexamethasone plasma cortisol concentration < 50% of the basal plasma cortisol concentration; and (3) an 8-hour post-dexamethasone plasma cortisol concentration < 50% of the basal plasma cortisol concentration. Any 1 of these results was considered evidence of adrenal suppression in response to the low-dose dexamethasone test.

To be included in this study, each dog must also have had blood samples collected before, and 4 and 8 hours after, IV administration of 0.1 mg of dexamethasone/kg (high-dose test). This test was also begun between 7:45 and 9:00 AM on a day that other testing of any kind was not performed and more than 24 hours after completion of the low-dose dexamethasone test. In response to the high-dose test, 4 criteria were used to discriminate PDH from ATH. These 4 criteria included: (1) a 4-hour post-dexamethasone plasma cortisol concentration < 1.4 µg/dl; (2) a 4-hour post-dexamethasone plasma cortisol concentration < 50% of the basal plasma cortisol concentration; (3) an 8-hour post-dexamethasone plasma cortisol concentration < 1.4 µg/dl; and (4) an 8-hour post-dexamethasone plasma cortisol concentration < 50% of the basal plasma cortisol concentration. Any 1 of these results was considered evidence of adrenal suppression in response to high-dose dexamethasone test.

Hormone assays—Blood samples obtained for determination of plasma cortisol concentration were placed in heparinized glass tubes and then were centrifuged. The plasma was frozen at −20 C until assayed. Plasma cortisol concentrations were determined by a previously validated enzyme immunoassay.[21] Blood samples obtained for determination of plasma endogenous ACTH concentrations were collected, stored, and assayed as previously described.[7,21]

Results

Dogs—The criteria for inclusion in this study were met by 216 dogs with hyperadrenocorticism. These included 35 dogs with adrenocortical tumors (13 adenomas and 22 carcinomas) and 181 dogs with PDH. Twenty-two of the 181 dogs with PDH had a mass in the area of the pituitary gland, as identified on brain CT scans (45/181 dogs with PDH assessed) and 25 had a mass in the area of the pituitary gland, as identified on MRI (41/181 dogs with PDH were assessed). Forty-three of the 181 dogs with PDH died. In these dogs, necropsy findings included a pituitary tumor with bilateral adrenocortical hyperplasia or mitotane-induced adrenocortical destruction. Rapid response to mitotane therapy was documented in 173 dogs. In dogs with PDH, adrenocortical tumors were not observed.

Low-dose dexamethasone—In response to the low-dose test, 213 of the 216 (99%) dogs had an 8-hour post-dexamethasone plasma cortisol concentration ≥ 1.4 µg/dl, thereby screening positive for hyperadrenocorticism. One hundred eleven of the 216 (51%) dogs met at least 1 of the 3 criteria for suppression by use of the low-dose test. Fifty-one of the 216 (24%) dogs had a plasma cortisol concentration < 1.4 µg/dl, 4 hours after dexamethasone administration. One hundred two of the 216 (47%) dogs had a plasma cortisol concentration < 50% of the basal cortisol concentration, 4 hours after dexamethasone administration. Forty-four of the 216 (20%) dogs had a plasma cortisol concentration < 50% of the basal cortisol concentration, 8 hours after dexamethasone administration.

Of the 35 dogs with ATH, none demonstrated suppression in response to the low-dose dexamethasone test, using any of the 3 criteria. Of the 181 dogs with PDH, however, 111 (61%) met at least 1 of the 3 criteria for suppression. One hundred two (56%) of the dogs with PDH had a plasma cortisol concentration < 50% of the basal concentration, 4 hours after dexamethasone administration. Fifty-one (28%) of the dogs with PDH had a plasma cortisol concentration < 1.4 µg/dl, and 44 (24%) had a plasma cortisol concentration < 50% of the basal concentration, 8 hours after dexamethasone administration.

High-dose dexamethasone—Of the 216 dogs with hyperadrenocorticism, 137 (63%) had results that indicated suppression in response to the high-dose dexamethasone test. Two of the 35 (6%) dogs with ATH had results that indicated suppression in response to the high-dose dexamethasone test. One dog with ATH had plasma cortisol concentrations of 3.1, 3.0, and 1.5 µg/dl, and the other dog had values of 1.5, 1.5, and 1.3 µg/dl (basal, 4, and 8 hours after dexamethasone administration, respectively).

Of the 181 dogs with PDH, 135 (75%) had high-dose test results indicative of suppression, as defined by at least 1 of the 4 criteria used. Criteria for suppression were satisfied at both 4 and 8 hours after dexamethasone administration in 115 dogs with PDH. Evidence of suppression, on the basis of at least 1 of the two 4-hour post-dexamethasone high-dose results (but neither 8-hour test result) was observed in 11 dogs with PDH, 7 of which had previous results indicative of suppression in response to the low-dose test. Evidence of suppression, on the basis of at least one 8-hour post-dexamethasone high-dose test result (but neither 4-hour test result) was observed in 9 dogs with PDH, 6 of which had previous results indicative of suppression in response to the low-dose test.

Of the 111 dogs with PDH that had test results that indicated suppression after receiving low-dose dexamethasone, 109 also had results that indicated suppression in response to the high-dose test. Two dogs had apparently contradictory results (evidence of suppression in response to the low-dose test but not the high-dose test). In both, plasma cortisol concentrations in response to the high-dose test were borderline for suppression (basal, 4-, and 8-hour values: 2.5, 1.5, 1.4 µg/dl and 2.2, 1.4, and 1.5 µg/dl in the 2 dogs, respectively).

In addition to the 109 dogs with PDH that had test results indicative of suppression after administra-

tion of both low and high doses of dexamethasone, 26 dogs with PDH that did not have evidence of suppression after receiving the low-dose test, did respond to the high-dose test (14% of the 181 dogs with PDH). Forty-four of the 181 (24%) dogs with PDH did not have test results indicative of suppression after receiving low or high doses of dexamethasone. The diagnosis of PDH was supported by identification of a pituitary mass in 38 of these 44 dogs on CT scans (8 dogs), MRI scans (12 dogs), or at necropsy (18 dogs). Three of these 44 dogs did not have a pituitary mass identified at necropsy, but each had bilateral adrenocortical hyperplasia. Each of these 44 dogs also had an endogenous plasma ACTH concentration > 50 pg/ml and relatively equal-sized adrenal glands identified by use of abdominal ultrasonography.

Discussion

It is generally agreed that naturally developing hyperadrenocorticism in dogs should first be suspected from abnormalities identified on history and physical examination.[4,5] This tentative diagnosis should be supported by finding typical abnormalities of hyperadrenocorticism on a CBC, serum biochemical analysis, urinalysis, and abdominal ultrasonography or radiography. Endocrine screening tests are then used to confirm the diagnosis of hyperadrenocorticism. Each of the commonly used screening tests for hyperadrenocorticism in dogs (low-dose dexamethasone test, ACTH stimulation test, and urine cortisol/creatinine ratio) have positive and negative attributes.[4,5,b]

The low-dose dexamethasone screening test is a sensitive test for hyperadrenocorticism, inexpensive, easily performed, does not require sophisticated facilities, and interpretation of test results is usually straightforward. However, this test does require 2 or 3 blood samples to be obtained over a period of 8 hours, is not completely specific (some dogs with nonadrenal disease have positive test results), and sometimes has test results that are considered vague or borderline.[19,b]

Data from this study confirmed results previously reported, namely that measurement of the plasma cortisol concentration 8 hours after administration of a low dose of dexamethasone is a helpful screening test for hyperadrenocorticism.[20] Also in this study, plasma cortisol concentrations obtained 4 and 8 hours after administering a low dose of dexamethasone to dogs with hyperadrenocorticism helped to distinguish PDH from ATH. Using any of the 3 criteria for adrenal suppression, 111 of the 216 (51%) dogs with hyperadrenocorticism responded to low-dose dexamethasone. None of the dogs with ATH responded to low-dose dexamethasone. Thus, the 111 responders to the low-dose test included 61% of the dogs with PDH. A 4-hour plasma cortisol concentration < 50% of the basal concentration provided the most sensitive low-dose test result for suppression. However, low-dose test results from more than 30 dogs met each of the other 2 criteria for adrenal suppression. Thus, in a dog with hyperadrenocorticism, failure to meet any of these 3 criteria in response to low-dose dexamethasone should be interpreted as inconclusive with respect to discriminating PDH from ATH. Suppression, however, in response to the low-dose test, as defined herein, should be considered strong evidence of PDH in dogs.

A total of 135 dogs with PDH had plasma cortisol concentrations indicative of adrenal gland suppression after administration of high-dose dexamethasone. Plasma cortisol concentrations met the criteria for suppression in 115 dogs with PDH at both the 4- and 8-hour post-dexamethasone time periods. Nine dogs with PDH (plus 2 dogs with ATH) had plasma cortisol concentrations that met criteria for suppression at 8 hours after dexamethasone administration, but not at 4 hours. Six of these 9 dogs also had plasma cortisol concentrations that indicated suppression after low-dose dexamethasone. Thus, only 3 of 216 (1%) dogs had an 8-hour high-dose dexamethasone test result that provided information not obtained previously from the low-dose test results, or from the 4-hour high-dose test result.

Eleven of the 216 dogs in this study had plasma cortisol concentrations that met criteria for suppression at 4 hours after high-dose dexamethasone administration, but not at 8 hours. Seven of these 11 dogs had plasma cortisol concentrations that indicated suppression after receiving low-dose dexamethasone. Thus, only 4 of 216 (2%) dogs had a 4-hour high-dose dexamethasone test result that provided information not obtained from the low-dose test or from the 8-hour high-dose test result.

The results of high-dose dexamethasone testing in the 216 dogs with hyperadrenocorticism confirms results previously reported.[4,5,7] Two of the 35 dogs with ATH had borderline high-dose results, thereby indicating that responses to high-dose dexamethasone cannot be considered absolute. One hundred thirty-five of the 181 (75%) PDH dogs met at least 1 of the 4 criteria for adrenal suppression, and therefore, suppression in response to the high-dose test can be considered strong evidence of PDH in a dog with hyperadrenocorticism. However, of those 135 dogs, 109 (81%) had previously demonstrated suppression in response to the low-dose dexamethasone test. The high-dose dexamethasone test results provided additional information in only 26 of 216 (12%) dogs. These data suggest that the low-dose dexamethasone test can be used in dogs to screen for hyperadrenocorticism and to discriminate ATH from PDH. It is therefore recommended that veterinarians obtain a basal, 4-, and 8-hour blood sample after low-dose dexamethasone administration from dogs suspected clinically of having hyperadrenocorticism. If the 8-hour low-dose test result is consistent with the diagnosis of hyperadrenocorticism, and the plasma cortisol concentrations at 4 or 8 hours meet criteria established for PDH, treatment for this condition can be recommended to the owner. If suppression in response to low-dose dexamethasone is not found, the diagnosis of hyperadrenocorticism would be supported, but further testing would be required to distinguish PDH from ATH. These additional tests may include abdominal radiography or ultrasonography, determination of plasma endogenous ACTH concentrations, or response to high-dose dexamethasone.

[a]Cortrosyn, Organon Diagnostics Inc, West Orange, NJ.

[b]Kaplan AJ, Peterson ME, Kemppainen RJ. Effects of nonadrenal disease on the results of diagnostic tests for hyperadrenocorticism (abstr), in *Proceedings*. Twelfth Annu Vet Med Forum 1994;992.

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Books Received

Receipt of these books is acknowledged. Listing should be regarded as a return of courtesy to the sender. Books that appear to be of particular interest will be reviewed as space permits.

The Veterinary Clinics of North America: Equine Practice. Clinical Pathology. Vol 11, December 1995. Nat T. Messer, Guest Editor. 553 pages; illustrated. WB Saunders Co, The Curtis Center, Independence Square West, Philadelphia, PA 19106-3399. Subscription price: $79.00, individuals; $96.00, institutions.

The Veterinary Clinics of North America: Small Animal Practice. Canine and Feline Transfusion Medicine. Vol 25, November 1995. Annemarie Kristensen and Bernard Feldman, Guest Editors. 1490 pages; illustrated. WB Saunders Co, The Curtis Center, Independence Square West, Philadelphia, PA 19106-3399. Subscription price: $93.00, individuals; $111.00, institutions.

Formulary for Laboratory Animals. Compiled by C. Terrance Hawk and Steven Leary in association with the American College of Laboratory Medicine. 101 pages. Iowa State University Press, 2121 S State Ave, Ames, IA 50014-8300. 1995. Price $17.95.

A Manger in my Rabbit. Memoirs of an Oregon Veterinarian. By Robert Whittaker, DVM. 226 pages. Vantage Press Inc, 516 W 34th St, New York, NY 10001. 1995. Price $16.95.

Color Atlas of The Horse's Foot. By Christopher C. Pollit. 208 pages; illustrated. Mosby-Wolfe, an imprint of Times Mirror International Publishers Ltd, 7-12 Tavistock Square, London WCIH 9LB, England. Available in the United States from Mosby-Year Book Inc, 11830 Westline Industrial Dr, St Louis, MO 63146-3318. 1995. Price $99.95.

Videotape

Video for Small Animal Practitioners. The Waltham Forum. Vol 7. No. 4. 1995. Topics: Gastrointestinal Endoscopy: Intestine; Systemic Hypertension in Cats; Case Study: Diabetes Mellitus in a Cat; Hyperlipidemia in Dogs; Therapy of Common Cardiac Arrhythmias. Veterinary Learning Systems, 425 Phillips Blvd, #100, Trenton, NJ 08618. Subscription price: 4 issues/$86.95.