JAVMA

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Adrenocortical hemorrhage following intravenous tetracosactide in a dog with hypercortisolism

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Received July 28, 2023
Accepted October 12, 2023

doi.org/10.2460/javma.23.07.0391

OBJECTIVE
To summarize findings from a case of adrenocortical hemorrhage following tetracosactide injection during ACTH stimulation testing for monitoring of trilostane therapy in a dog.

ANIMAL
A 12-year old neutered male dog with adrenal-dependent hypercortisolism.

CLINICAL PRESENTATION, PROGRESSION, AND PROCEDURES
4 hours after ACTH stimulation testing, the patient developed vomiting, lethargy, and abdominal pain. Abdominal ultrasound was performed before and after an ACTH stimulation test. Following ACTH stimulation testing, there was progressive bilateral adrenal enlargement and free abdominal fluid had developed. This was considered to be caused by adrenocortical inflammation and hemorrhage secondary to the synthetic ACTH analog, tetracosactide, used during stimulation testing. A resting cortisol performed 5 hours after tetracosactide injection was not consistent with iatrogenic hypoadrenocorticism.

TREATMENT AND OUTCOME
The patient was managed with analgesia, IV fluids, and corticosteroids and made a full recovery.

CLINICAL RELEVANCE
To the authors' knowledge, this was the first reported case of adrenocortical hemorrhage following administration of a synthetic ACTH analog in a dog. This should be considered as a rare potential complication of ACTH stimulation testing.

Keywords: hypercortisolism, adrenal, trilostane, dog, endocrine

History

A 12-year-old neutered male Beagle presented for routine monitoring of trilostane therapy. Hypercortisolism was diagnosed 6 months earlier with compatible clinical signs and confirmatory low-dose dexamethasone suppression test. On initial abdominal ultrasound, the right and left adrenal gland caudal pole widths measured 1.55 and 0.34 cm, respectively. Adrenal-dependent hypercortisolism was suspected given the significant adrenal asymmetry and the contralateral gland measuring < 0.5 cm in width. Surgery was discussed as the only potentially curative treatment; however, due to associated risks the owner elected to proceed with medical management. The dog was started on trilostane PO (Vetoryl) at 30 mg (1.7 mg/kg) twice daily. ACTH stimulation testing (ACTHS) was performed with 5 μg of Synacthen/kg IV (tetracosactide) 1 month after starting trilostane (ACTHS started 4 hours following trilostane dosing). Pre- and post- tetracosactide cortisol concentrations were 21 and 71 nmol/L (reference interval [RI], 30 to 100 nmol/L). Over the next 3 months, clinical signs of hypercortisolism improved and the patient was reportedly systemically well.

At routine revisit 4 months after starting trilostane, the patient was doing well. An abdominal ultrasound, CBC, serum biochemistry, and ACTHS were performed (started 4 hours after trilostane dosing, protocol as outlined above). Adrenal sizes were similar to previous measurements (right, 1.97 cm **[Figure 1]**; left, 0.35-cm caudal pole width). No other significant abnormalities were reported on the ultrasound. Hematology revealed a leukocytosis (18.4

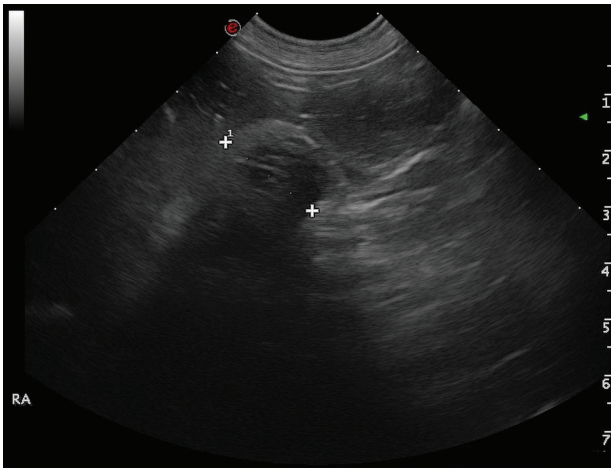

Figure 1—Right adrenal gland measured prior to ACTH stimulation testing (ACTHS). Caudal pole width measures 1.97 cm.

X 10^9/L; RI, 6.0 X 10^9 to 14.0 X 10^9/L) with a neutrophilia (16.6 X 10^9/L; RI, 4.1 X 10^9 to 9.4 X 10^9/L) and mild ALP elevation (231 U/L; RI, 1 to 120 U/L). All other results were within RI. The dog was discharged later that day while awaiting results.

Approximately 4 hours after discharge, the patient re-presented with vomiting and lethargy. On physical examination, there was abdominal pain, mild pyrexia (39.1 °C), and tachycardia (140 beats/min).

Diagnostic Findings and Interpretation

The results of the ACTHS performed the morning the patient became unwell returned the following day with cortisol concentrations of 23 nmol/L (pre) and 50 nmol/L (post).

An abdominal ultrasound was performed when the patient re-presented systemically unwell that afternoon, approximately 4 hours after the abovementioned ACTHS. The ultrasound showed an increase in the size of the left (0.56-cm caudal pole width) and right (4.97-cm length X 2.57-cm caudal pole width; **Figure 2**) adrenal gland compared to the pre-ACTH sonographic findings. There was free fluid and hyperechoic mesentery surrounding the right adrenal gland. Findings were concerning for adrenalitis, adrenocortical necrosis or hemorrhage, thromboembolic disease, or atypical presentation of anaphylaxis.

Blood was submitted for cortisol concentration; no other testing was performed.

Treatment and Outcome

The dog was commenced on IV fluids (lactated Ringer) and a fentanyl infusion. Dexamethasone 0.1 mg/kg was given IV for presumed adrenocortical necrosis and adrenalitis. Dalteparin (150 IU/kg, SC, q 8 h) was also given to reduce the risk of thromboembolism. The cortisol concentration returned sufficient to exclude iatrogenic hypoadrenocorticism (176 nmol/L).

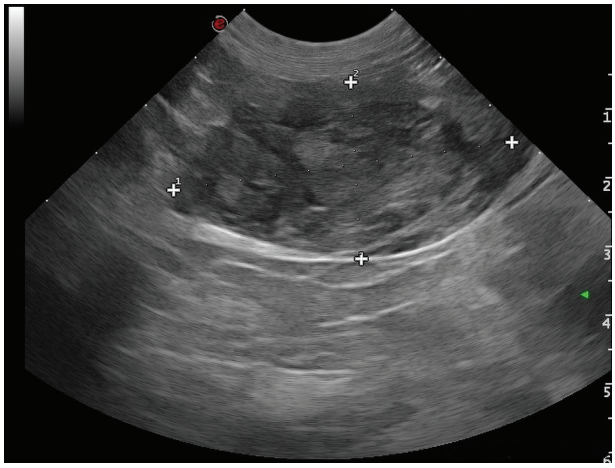

Figure 2—Right adrenal gland following ACTHS. Caudal pole width measures 2.57 cm.

The dog improved overnight and was discharged the next day on prednisolone at 7.5 mg once daily (0.5 mg/kg). Trilostane was discontinued. The prednisolone dose was gradually tapered and discontinued over the following week.

One week later, the dog was reportedly well but with recurrence of prehypercortisolism treatment polyuria and polydipsia. Abdominal ultrasound revealed reduction in the size of the right adrenal gland (up to 1.94 cm at the caudal pole; **Figure 3**) with a

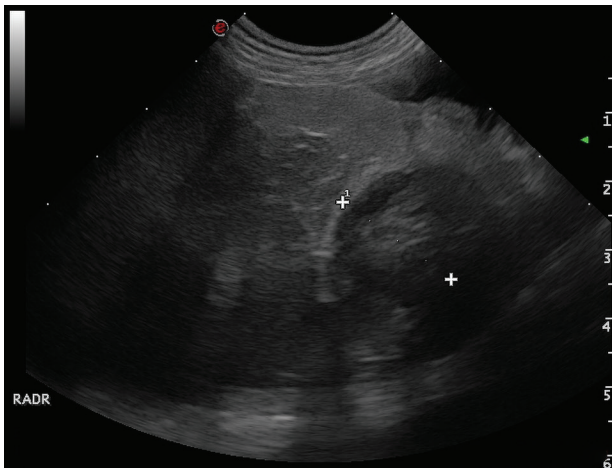

Figure 3—Right adrenal gland 1 week following ACTHS. Caudal pole width measures 1.94 cm.

persistent, large heterogenous region located caudal to the right adrenal gland. Blood was submitted for a CBC and serum biochemistry, which revealed a leukocytosis (18.4 X 10^9/L; RI, 6.0 X 10^9 to 14.0 X 10^9/L), neutrophilia (16.6 X 10^9/L; RI, 4.1 X 10^9 to 9.4 X 10^9/L), and ALP elevation (231 U/L; RI, 1 to 120 U/L). Remaining results were within RI. Despite discontinuation of prednisolone, 12 days after the event, clinical signs including polyuria and polydipsia persisted and the dog was restarted on a lower trilostane dose of 25 mg (1.4 mg/kg) twice daily. A compounded tablet (BOVA Compounding) was used due to the lack of availability of a commercial product at this dose. On-

going monitoring of trilostane therapy was performed using 3-hour post-trilostane cortisol concentration.[1]

Comments

To the authors' knowledge, this was the first documented case in the veterinary literature of adrenocortical hemorrhage following administration of a synthetic ACTH (sACTH) analog, Synacthen (tetracosactide).

ACTHS is frequently performed by clinicians in both the diagnosis of hypercortisolism and monitoring of trilostane therapy, although the optimal method for monitoring effective trilostane therapy remains controversial.[1] Reported adverse effects of sACTH in humans and animals are rare; however, isolated reports of adrenal hemorrhage are reported following administration of sACTH in people.[2]

In rats, administration of sACTH at doses of 10 to 60 μg/d has been shown to induce dose-dependent adrenocortical hemorrhage, vacuolization, and apoptosis. When treated with trilostane, however, rats did not develop these lesions.[3] Adrenal hemorrhage has been reported in dogs treated with trilostane.[4] It is unclear whether this is a direct effect of trilostane or its metabolites on the adrenal gland, or due to disinhibition of cortisol-induced decreases in endogenous ACTH concentration. If the latter were true, low cortisol concentrations (as seen with tight control of hypercortisolism) could result in elevated endogenous ACTH (eACTH) concentrations due to loss of negative feedback. This may predispose patients to develop adrenocortical hemorrhage when administered sACTH. Finally, elevated levels of eACTH and catecholamines have been proposed as contributing factors in nontraumatic adrenal hemorrhage, which may occur as a result of critical illness.[5]

In this case, adrenocortical hemorrhage is suspected, given the acute onset of signs following an ACTHS and consistent imaging findings. One limitation was that a definitive diagnosis was not able to be confirmed with cytology or histopathology. However, most reported human cases are diagnosed on the basis of a combination of diagnostic imaging findings (typically CT) and hormone measurements (ACTH).[2] In this case, given the suspicion for adrenocortical hemorrhage and/or necrosis, the risks of attempting adrenal aspiration were not considered to be in the patients' best interests. Furthermore, given the rapid response to supportive care, further investigation was not performed.

Nontraumatic adrenal hemorrhage would also be a possible differential for the sonographic changes in this patient; however, as this condition typically occurs in critically ill patients,[2] it is considered less likely. A thromboembolic event is also possible; however, a thrombus was not seen sonographically. Anaphylaxis unrelated to ACTH administration is also possible; however, there was no supporting history or other findings, such as gall bladder wall edema, to support this.

In this case, the strong temporal association between administration of sACTH and the rapid and marked change in the right adrenal gland on ultrasound suggest that the presumed adrenocortical hemorrhage was likely related to administration of sACTH. It is possible that prior treatment with trilostane contributed to elevated ACTH levels; however, eACTH was not measured in this case, which was a limitation. It is also possible that spontaneous adrenal hemorrhage occurred independent of sACTH; however, this appears less likely given the clinical progression.

It is unclear whether adrenal hemorrhage in this case represents an idiosyncratic or dose-dependent reaction to tetracosactide; however, the authors elected to avoid further administration in this patient. Ongoing monitoring was achieved by use of the 3-hour post-trilostane cortisol measurement as previously reported.[1] Concurrent measurement of the pretrilostane cortisol would have improved follow-up monitoring[1] but was not performed. The dose of tetracosactide used in this study (5 μg/kg) is widely used as part of standard protocol for ACTH stimulation testing; however, as effects on adrenal glands may be dose dependent,[3] use of a lower dose may be more appropriate. A dose of 1 μg/kg tetracosactide has been shown to be similarly effective (compared to 5 μg/kg) for monitoring of trilostane therapy for hypercortisolism in dogs.[6]

As adrenal hemorrhage is a poorly reported condition in veterinary patients, optimal treatment is not established. In human medicine, treatment includes prompt administration of glucocorticoids, with the addition of mineralocorticoid, IV fluids, and other symptomatic treatment if suspicious for a hypoadrenocortical crisis.[5] In this case, at the time of presentation, an anticoagulant was used to reduce risk of thromboembolism; however, this may not have been appropriate and may have perpetuated adrenal hemorrhage. Additionally, it should be noted that a compounded trilostane product was used in this patient to facilitate a small dose reduction. Veterinarians should be aware that pharmacokinetic properties may differ between compounded and licensed products and that the latter should be used whenever possible.

To the authors' knowledge, this report documents the first case of adrenocortical hemorrhage following administration of an sACTH analog for routine monitoring of trilostane therapy. While extremely rare, clinicians should be aware of the risk of adrenocortical hemorrhage in dogs that become unwell within several hours of an ACTHS.

Acknowledgments

None reported.

Disclosures

The authors have nothing to disclose. No AI-assisted technologies were used in the generation of this manuscript.

Funding

The authors have nothing to disclose.

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