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Canine iatrogenic persistent hypoadrenocorticism after short-term treatment of hyperadrenocorticism with trilostane - a case report

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ABSTRACT

An 8-year-old, spayed female, mixed breed dog diagnosed with hyperadrenocorticism and treated with trilostane for 13 days was presented to the clinic due to vomiting, shaking, and weakness. The ACTH stimulation test and electrolyte analysis confirmed hypoadrenocorticism. Treatment with prednisolone and fludrocortisone gave good results, however long lasting exogenous glucocorticoid administration led to a decrease in total and free thyroxine concentrations and caused clinical signs of hypothyroidism, such as lethargy and reduced appetite. The authors suspected euthyroid sick syndrome. After sixteen months therapy with prednisolone and fludrocortisone ACTH stimulation tests still revealed low plasma cortisol concentrations in this dog, which suggested persistent hypoadrenocorticism. To the authors' knowledge there have only been a few cases in which canine iatrogenic persistent hypoadrenocorticism or hypocortisolism was described after short term treatment with trilostane. However, in the previous cases the longest duration of hypocortisolism was 12 months.

Key words: canine Addison's disease, iatrogenic hypoadrenocorticism, trilostane

Introduction

Canine hypoadrenocorticism (Addison's disease) is a disease resulting from the deficient production and secretion of gluco- and/or mineralocorticoids by the adrenal glands. Two major forms of canine hypoadrenocorticism have been described: primary hypoadrenocorticism due to a lesion in the adrenal cortices, and secondary hypoadrenocorticism (hypocorticolism) due to insufficient production of ACTH by the

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pituitary gland (GALAC et al., 2010). There are also forms of iatrogenic adrenocortical insufficiency caused by: prolonged glucocorticoid therapy leading to suppression of the hypothalamic-pituitary-adrenocortical axis or due to treatment with mitotane, which can cause necrosis of the zona fasciculata and zona reticularis in the adrenal glands (WILLARD et al., 1982; PLUMB, 2008a; GALAC et al., 2010).

Trilostane is an adrenal steroid synthesis inhibitor. It reduces synthesis of cortisol, aldosterone and adrenal androgens. Development of hypoadrenocorticism is one of the most serious adverse effects. Therefore, monitoring of therapy with trilostane is recommended (PLUMB, 2008b; KOOISTRA, 2010). The purpose of this case report is to show how important monitoring is in the treatment of hyperadrenocorticism with trilostane, and to show that even very brief therapy may lead to persistent Addison's disease.

Case history

History. An 8-year-old, 10 kg spayed female, mixed breed dog was presented to the Centre of Small Animal Health - Clinic Multiwet with a 4-week history of polyuria, polydipsia and was diagnosed with hyperadrenocorticism. Two weeks earlier an ACTH stimulation test was performed in another clinic. Hyperadrenocorticism was suspected due to the elevated ALP (1135 U/L). Diagnosis of hyperadrenocorticism was based on increased plasma cortisol concentrations (1379 nmol/L) 60 min after ACTH administration (reference interval for the test, 270 to 690 nmol/L). The referring veterinarian administered trilostane (Vetoryl®, Janssen Animal Health) at the initial dose of 2 mg/kg PO once a day for 10 days and then the dose was increased to 4 mg/kg daily in one dose. After 2 doses of 4 mg/kg the dog lost appetite. After the third higher dose of trilostane the owner of the dog observed clinical signs such as vomiting, shaking, and weakness.

Clinical exam findings. At presentation at the Centre of Small Animal Health - Clinic Multiwet physical examination of the dog revealed heart rate, respiratory rate and temperature within reference intervals (112 beats/min, 38 breaths/min, and 37.9 °C, respectively). The mucous membranes were dry and pale, and the skin turgor was decreased. The dog was estimated to be 5% dehydrated and suffering from abdominal pain.

Laboratory results. Initial diagnostic tests included a complete blood count (CBC), serum biochemical profile, electrolyte analysis and ACTH stimulation test (tetracosactide 0.25 mg/dog, IM, Synacthéne, Defiante Farmaceutica). Results from the ACTH stimulation test and electrolyte analysis revealed decreased plasma cortisol concentrations: <27.6 nmol/L 60 min after tetracosactide administration (reference interval for the test, 270 to 690 nmol/L), hyponatremia (sodium 130.5 mmol/L; reference interval, 139.1 to 156.5 mmol/L) and hyperkalemia (potassium 6.7 mmol/L; reference interval, 4.1 to 5.4 mmol/

L). The sodium:potassium (Na:K) ratio was decreased at 19.5 (reference interval, 27 to 40). Results from the CBC demonstrated leukocytosis (22.5 G/L; reference interval, 6.0 to 14 G/L), neutrophilia with a left shift (segmented neutrophils count 18.45 G/L; reference interval, 2.9 to 12 G/L; non-segmented neutrophils count 1.8 G/L; reference interval, 0.0 to 0.45 G/L), and mild anemia (red blood cell count 5.35 T/L; reference interval, 5.5 to 8.0 T/L; hemoglobin concentration 7.9 mmol/L; reference interval, 7.45 to 11.17 mmol/L; hematocrit 0.36 L/L; reference interval, 0.37 to 0.55). However, the severity of anemia might have been masked by hemoconcentration due to dehydration. On serum biochemical profile, mild hypoglycemia (66 mg/dL; reference interval, 70 to 120 mg/dL), mild azotemia (creatinine 1.9 mg/dL; reference interval, 1.0 to 1.7 mg/dL; urea 112 mg/dL; reference interval, 20 to 45 mg/dL), mildly elevated alkaline phosphatase (ALP 267 U/L; reference interval, 20 to 155 U/L), moderately elevated alanine aminotransferase (ALT 222 U/L; reference interval, 3 to 50 U/L), and mildly elevated total serum protein concentration (76 g/L; reference interval, 55 to 70 g/L) were noted.

Diagnosis of iatrogenic hypoadrenocorticism was based on the results of the ACTH stimulation test, electrolyte analysis and decreased Na:K ratio.

Therapy. For the initial treatment, a single dose of dexamethasone (Dexasone, ScanVet Poland), 0.5 mg/kg, IV; buprenorphine (Bunondol, Warszawskie Zakłady Farmaceutyczne Polfa), 10 μg/kg, IV; metoclopramide (Metoclopramidum, Polpharma), 0.25mg/kg, SC, q6h; 0.9% saline (Natrium Chloratum 0,9%; Polfa Lublin), 15 mL/kg, IV, q6h; and 5% glucose (Injectio Glucosi 5%, Polfa Płyny), 15 mL/kg, IV, q 6h, were administered the first day. Fluid therapy was continued for 3 days, and antiemetic and analgesic therapy for 1 day. Concurrently the dog had been given fludrocortisone (Cortineff, Polfa Pabianice), 0.01 mg/kg, PO, q12h for 3 days, and prednisolone (Encortolon, Polfa Pabianice), 0.5 mg/kg, PO, q24h for 2 days.

After 3 days of therapy, the dog's heart rate, respiratory rate, and temperature were within reference intervals. The dog ate spontaneously and had normal vital signs. Biochemistry revealed hyponatremia (sodium 133.7 mmol/L; reference interval, 139.1 to 156.5 mmol/L) and normokalemia (potassium 5.0 mmol/L; reference interval, 4.1 to 5.4 mmol/L). However, the Na:K ratio was still mildly decreased at 26.7 (reference interval, 27 to 40). The dog had still leukocytosis (24.0 G/L), mild anemia, and increased ALP and ALT activity. Glucose, creatinine and urea concentrations were within reference intervals. The patient was discharged after 3 days of hospitalization. Fludrocortisone (Cortineff, Polfa Pabianice), 0.01 mg/kg, PO, q12h for 7 days and prednisolone (Encortolon, Polfa Pabianice), 0.5 mg/kg, PO, q24h for 7 days were prescribed for treatment of the hypoadrenocorticism, and amoxicillin with clavulanic acid (Synulox, Pfizer) 12.5 mg/kg, PO, q12h, for 7 days because of leukocytosis.

After a week the dog was in a good condition. Biochemistry revealed mild hyponatremia (sodium 138.6 mmol/L), hyperkalemia (potassium 6.1 mmol/L), decreased Na:K ratio (22.7), normoglycemia, mild leukocytosis (15.5 G/L) and mild anemia (red blood cell count 5.4 T/L; hemoglobin concentration 7.9 mmol/L; hematocrit 0.35 L/L). Fludrocortisone and prednisolone were continued for next 7 days, and after that time, sodium and potassium concentration were within reference intervals (sodium 141.6 mmol/L; potassium 5.3 mmol/L). However Na:K ratio was still mildly decreased (26.7).

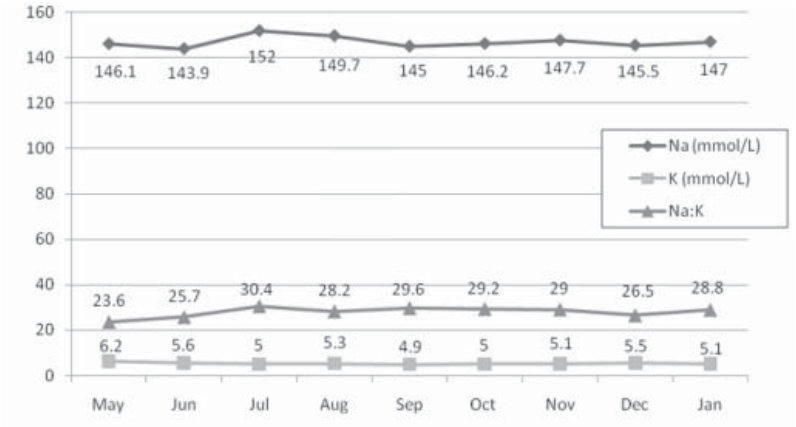

Fig. 1. Sodium and potassium concentration (mmol/L) measured in the serum of the dog once a month between May 2008 and January 2009 (Na, sodium concentration; K, potassium concentration; Na:K, sodium: potassium ratio)

Fludrocortisone therapy (Cortineff, Polfa Pabianice), 0.01 mg/kg, PO, q12h and prednisolone therapy (Encortolon, Polfa Pabianice), 0.5 mg/kg, PO, q24h, were continued for the next 9 months. Sodium and potassium concentrations were measured once a month (Fig. 1). After this period an ACTH stimulation test was performed again. Results from the test revealed low plasma cortisol concentration (81 nmol/L) 60 min after tetracosactide administration (Synacthéne, Defiante Farmaceutica). A diagnosis of persistent stable hypoadrenocorticism was made. Fludrocortisone and prednisolone therapies were still continued for the next 5 months, and sodium and potassium concentrations were measured once every 2 months. The Na:K ratio, sodium and potassium concentrations were within reference intervals and the dog was in good condition.

The owner of the dog observed lethargy and reduced appetite in the dog. Clinical examination did not reveal any abnormalities. Diagnostic tests included a CBC, serum biochemical profile, electrolyte analysis, ACTH stimulation test, and abdominal ultrasound examination. The laboratory tests revealed only low plasma cortisol concentration after

tetracosactide administration (Synacthéne, Defiante Farmaceutica). The Na:K ratio, sodium and potassium concentration were within the reference interval. Biochemical and CBC tests did not reveal any abnormalities. Abdominal ultrasonography revealed hepatomegaly and small, hyperechoic adrenal glands (diameter 2.8 mm). Tests for levels of total thyroxine (tT4), free thyroxine (fT4) were performed and revealed a decrease in tT4 and fT4 concentrations (tT4, 8.1 ng/mL; reference interval, 15 to 40 ng/mL; fT4, 0.87 ng/dL; reference interval, 1 to 4 ng/dL). A suspicion of euthyroid sick syndrome as a result of glucocorticoid therapy was made.

ACTH stimulation test was performed four weeks later and revealed low plasma cortisol concentration (96 nmol/L) 60 min after tetracosactide administration.

Discussion

There have been a few cases in which canine iatrogenic persistent hypoadrenocorticism or hypocortisolism were described after short term treatment with trilostane (CHAPMAN et al., 2004; RAMSEY et al., 2008). REUSCH et al. (2007) showed that dogs with hyperadrenocorticism treated with trilostane had variable degrees of adrenal necrosis. Also CHAPMAN et al. (2004) showed that trilostane therapy may lead to adrenal cortical necrosis. The mechanism of cell death in the adrenal glands after treatment with trilostane is unknown. REUSCH et al. (2007) hypothesized that trilostane or its metabolites may lead directly to necrosis and/or apoptosis. These authors suggested that in some dogs necrosis or apoptosis in the adrenal cortex may lead to adrenal insufficiency. Hypoadrenocorticism, as the result of cell death in the adrenal glands, may be observed in dogs treated with trilostane for a period longer than 15 months with mean trilostane dosage higher than 11.7 mg/kg daily and with a history of therapy with mitotane before treatment with trilostane. However, in this case report the dog was treated only 13 days with a lower dosage of trilostane and had not been treated with mitotane earlier. CHAPMAN et al. (2004) also observed clinical signs of hypoadrenocorticism and marked necrosis in the adrenal glands in a dog after trilostane therapy lasting only 22 days with a dosage 7.1 mg/kg daily. Moreover, that dog had not been treated with mitotane before the therapy with trilostane as well. A similar case report was described by RAMSEY et al. (2008). These authors observed clinical signs of hypoadrenocorticism after 3-day therapy with trilostane at a dose of 5 mg/kg daily. That dog had also not been treated with mitotane. Thus, it seems probable that even short-term trilostane therapy may lead to adrenal necrosis caused by direct action of trilostane or its metabolites. Yet, both CHAPMAN et al. (2004) and REUSCH et al. (2007) did not exclude an idiosyncratic reaction to the drug. The dog described in this case report was treated with trilostane for a very short period and developed clinical signs of adrenal insufficiency. It seems probable that this dog also had necrotic lesions in the adrenal glands after treatment with trilostane and these lesions might have led to hypoadrenocorticism. However, the owner of the dog eventually did not consent to biopsy of the adrenal glands.

The therapy with fludrocortisone and prednisolone allowed glucose, sodium and potassium levels to normalize. Clinical signs of hypoadrenocorticism also ceased after this therapy. However, probably the exogenous glucocorticoid administration caused euthyroid sick syndrome. This supposition may be confirmed by the results of the tests for levels of tT4 and fT4 (FELDMAN and NELSON, 2004).

Trilostane therapy seems to be a safer therapy than mitotane for canine hyperadrenocorticism. CLEMENTE et al. (2007) showed that dogs treated with trilostane tended to live longer than dogs treated with mitotane. In most dogs the drug is well tolerated. NEIGER et al. (2002) observed clinical signs of hypoadrenocorticism in only 2 out of 78 dogs treated with trilostane. Moreover, in one of these dogs signs of hypoadrenocorticism quickly resolved after the withdrawal of the drug. In the previous case report RAMSEY et al. (2008) described a dog with hypocortisolism after 3 doses of trilostane. In that case hypocortisolism persisted and progressed for more than 3 months despite immediate withdrawal of the trilostane. After prednisolone therapy the clinical signs of hypocortisolism resolved. However, that dog had sodium and potassium concentrations within reference intervals. Thus the dog had isolated hypocortisolism. In that dog prednisolone therapy was required for more than 1 year. However, in this case prednisolone had to be combined with fludrocortisone owing to the abnormal sodium and potassium concentrations and decreased Na:K ratio. Moreover, the therapy was continued for 16 months, and ACTH stimulation tests still revealed low plasma cortisol concentration, which suggested persistent hypoadrenocorticism. This case showed how important it is to monitor the treatment of hyperadrenocorticism with trilostane and also that even very brief therapy may lead to persistent Addison's disease probably caused by irreversible lesions in the adrenal glands.

KOOISTRA (2010) recommended initial treatment with trilostane at a dose of 2 mg/kg daily in one or two portions and adjusting the dose according to the clinical response and result of ACTH stimulation test performed 2 weeks after the start of the therapy. These recommendations are very good, however, according to the authors of this case report, it should be emphasized that ACTH stimulation test should be performed every time before increasing the dose of the drug. Moreover, it seems that administration of trilostane in two portions daily may be safer than in one portion.

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SAŽETAK

Kastrirana kuja, mješanka, u dobi od osam godina, s prethodno dijagnosticiranim hiperadrenokorticizmom, liječena trilostanom 13 dana, bila je dovedena na kliniku zbog povraćanja, drhtanja i slabosti. Podražaj ACTH-om i analiza elektrolita potvrdili su da je riječ o hipoadrenokorticizmu. Liječenje prednizolonom i fludrokortizonom dalo je dobre rezultate. Ipak dugotrajno davanje egzogenog glukokortikoida dovelo je do smanjenja koncentracije ukupnog i slobodnog tiroksina te je uzrokovalo kliničke znakove hipotiroidizma kao što su letargija i smanjeni apetit. Autori su posumnjali na eutiroidni sindrom. Nakon 16 mjeseci terapije prednizolonom i fludrokortizonom, ACTH podražajni testovi pokazivali su još uvijek nisku koncentraciju kortizola u plazmi te kuje što je upućivalo na perzistentni hipoadrenokorticizam. Dosada je opisano svega nekoliko slučajeva jatrogenoga perzistentnoga hipoadrenokorticizma ili hipokortizolizma nakon kratkotrajne primjene alostana. U prijašnjim slučajevima hipokortizolizam je najduže trajao 12 mjeseci.

Ključne riječi: Adisonova bolest, pas, jatrogeni hipoadrenokorticizam, trilostan