

RESEARCH ARTICLE



Diagnosis of Cushing's syndrome in a guinea pig (*Cavia porcellus*) applying the modified version of the low-dose dexamethasone-suppression test used in canines

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ABSTRACT

The low dose dexamethasone stimulation test (LDDST) is routinely used in canine medicine but in the few cases in guinea pigs diagnosed with hypercortisolism, the adrenocorticotrophic hormone (ACTH) stimulation test was used. The objective of the authors was to conduct a pilot study and find out if the standard test used in dogs can be used in this species.

A 4-year-old intact female hairless guinea pig showed bilaterally enlarged adrenal glands and high cortisol levels. Urine was collected and, after initial saliva sample collection, 0.01 mg*kg⁻¹ dexamethasone was administered. Saliva was collected with a 1 mL syringe to determine cortisol levels upon 2, 4 and 8 h after dexamethasone application.

The urine cortisol:creatinine ratio was above 465.4*10⁻⁶. Before applying dexamethasone, the cortisol level was 171 nmol*L⁻¹. 2 h after initial application, it was 79 nmol*L⁻¹, at 4 h it was 70 nmol*L⁻¹, and at 8 h it rose to 1,280 nmol*L⁻¹.

The LDDST used in canine medicine to diagnose hypercortisolism can be adapted to guinea pigs and yields results to diagnose Cushing's syndrome in this species. As dexamethasone is more accessible, cheaper and more sensitive than the ACTH stimulation test, it should be a preferred choice from all aspects.

KEYWORDS

LDDST, hypercortisolism, saliva, UCCP, adrenal gland hyperplasia, pituitary dependent

INTRODUCTION

Cushing's syndrome develops when the body gets exposed to excessive amounts of cortisol for a longer period of time. It is a well-defined disease in dogs, but very few cases have been

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documented in guinea pigs. The most common type in dogs, the pituitary-dependent hypercortisolism, occurs in 80–85% of the cases. This is mostly caused by a functional ACTH-secreting pituitary tumour. The excessive ACTH secretion causes bilateral adrenocortical hyperplasia and with this, excess glucocorticoid secretion (Nelson 2009; Melián 2010; Behrend 2016). The low dose dexamethasone suppression test (LDDST) is considered the test of choice for hypercortisolism in canines with a high sensitivity but moderate specificity (Bennaim 2018).

Pituitary and adrenal tumours leading to hypercortisolism are uncommon in guinea pigs (Hocker et al., 2017; Pignon and Mayer 2020). Ultrasonography can support the diagnosis of hypercortisolism and help differentiation between pituitary-dependent hypercortisolism, when showing enlargement, or adrenocortical tumours when showing anatomic abnormalities or masses. However, the dimensions of adrenal glands can vary widely even in healthy guinea pigs (Fuchs et al., 2011; Künzel and Mayer 2015).

Plasma basal cortisol values are $11.7 \mu\text{g} \cdot \text{dL}^{-1}$ ($322.8 \text{ nmol} \cdot \text{L}^{-1}$) but due to the biphasic peak at dawn and dusk, it has no diagnostic value to confirming hypercortisolism in guinea pigs (Fujieda et al., 1982; Liu and Matthews 1999; Hocker et al., 2017). There is a linear correlation between free cortisol levels in plasma and saliva, as they are transported unaltered into the salivary glands (Riad-Fahmy et al., 1982; Fenske 1996, 1997). Cortisol concentration levels are 10 times higher in plasma than in saliva (Nemeth et al., 2016). The non-invasive method of collecting saliva for cortisol measurements in non-anaesthetised guinea pigs has been validated by Fenske (1996, 1997). According to literature, saliva is easily collected in guinea pigs when cotton buds are placed parallel with the cheek teeth for at least 5 min and then centrifugated (Fenske 1996, 1997). Fenske took saliva samples from guinea pigs, injected 20 IU ACTH intramuscularly and resampled them after 4 h. Saliva collection is less stressful than blood draw and the cortisol rise induced by handling and stress are lower. Salivary cortisol levels in untreated guinea pigs ranged from 2 to $26 \text{ ng} \cdot \text{mL}^{-1}$ and were not dependent of the amount of saliva acquired (Fenske 1997).

Only a few cases of enlarged adrenal glands and even fewer of hypercortisolism in guinea pigs have been reported in which the diagnosis was either based on histopathological findings or the use of the ACTH stimulation test (Hocker et al., 2017; Pignon and Mayer 2020). Manning (1976) found three mentions of adenoma, carcinoma and an unidentified tumour in the adrenal gland in guinea pigs, when researching the literature. Sommerey et al. (2004) found an adenoma of the adrenal gland when examining 689 guinea pigs. Gaschen et al. (1998) diagnosed Cushing's syndrome in a 5-year-old guinea pig using ultrasonography, but no endocrine tests. Clinical signs were bilateral alopecia, apathy, obesity, hepatomegaly and polydipsia/polyuria (PD/PU). The animal also had an ureterolith and hydronephrosis in the left kidney. Surgery was undertaken to remove the ureterolith and the adrenal gland tumour was also removed, but

the animal died post-operatively. Histopathology showed both adrenal glands had adenomas, but only the left was enlarged. Successful adrenalectomy has been described in a study on laboratory guinea pigs unrelated to hypercortisolism (Kudsk et al., 1983). Fujieda et al. (1982) applied a high dose of $1 \text{ mg} \cdot \text{kg}^{-1}$ dexamethasone intraperitoneally, as did Banjanin et al. (2004) intravenously, to suppress cortisol concentrations in the plasma of guinea pigs. Zeugswetter et al. (2007) determined hypercortisolism using the ACTH stimulation test using saliva as described by Fenske (1997). The 4-year-old female guinea pig showed signs of bilateral, non-pruritic hair loss, polydipsia, less activity and weight loss despite normal appetite. The skin was thin and elastic. The animal was treated with $2 \text{ mg} \cdot \text{kg}^{-1}$ trilostane once daily, which was elevated to $4 \text{ mg} \cdot \text{kg}^{-1}$ on day 35 of the treatment and then to $6 \text{ mg} \cdot \text{kg}^{-1}$ on day 65. This caused inappetence and weight loss, so the dose was reduced to 2 mg twice daily (Zeugswetter et al., 2007). Bilek et al. (2019) also diagnosed Cushing's syndrome in a guinea pig with the ACTH stimulation test using saliva cortisol concentrations in a 4.5-year-old female guinea pig. Samples were taken twice daily for 3 consecutive days and ACTH stimulation tests were performed. Ultrasonography revealed ovarian cysts and an enlarged right adrenal gland. The animal showed signs of bilateral exophthalmos, alopecia, lethargy, poor body condition and respiratory distress, but no PD/PU. The guinea pig was euthanised 4 months later as the owner declined treatment. Necropsy showed an adrenocortical carcinoma on the right side and lung metastasis. Zaheer and Beaufrère. (2020) reported a 3.5-year-old female guinea pig with bilateral symmetrical alopecia, exophthalmos and PD/PU. Abdominal ultrasound revealed small bilateral adrenal glands. Saliva collection was more difficult than reported in previous papers, so the animal was anaesthetised for blood draw from the cranial vena cava. After recovery, it received $5 \mu\text{g} \cdot \text{kg}^{-1}$ of ACTH intramuscularly and blood draw was repeated an hour later. The ACTH stimulation test revealed elevated cortisol levels. The animal was treated with $2 \text{ mg} \cdot \text{kg}^{-1}$ trilostane orally twice daily which was then elevated to $4 \text{ mg} \cdot \text{kg}^{-1}$. Clinical signs resolved after a month. The owner discontinued trilostane then started giving the medicine again, and the dose of trilostane had to be raised to $4 \text{ mg} \cdot \text{kg}^{-1}$ twice daily. A mass was found during ultrasonography on the right adrenal gland. The animal passed away 27 months after presentation (Zaheer and Beaufrère 2020).

Differential diagnosis includes vitamin C deficiency, which can lead to elevated cortisol concentrations in the plasma and saliva and enlarged adrenal glands in guinea pigs (Enwonwu et al., 1995), as do oestradiol injections applied in spayed females (Garris 1986). Significant increase in cortisol levels is also seen when an animal is isolated from the known group and put together with an unknown individual or taken on long car rides (Fenske 1997; Henessy et al., 2000; Nemeth et al., 2016). Alopecia and thin skin can be caused by functional ovarian follicular cysts and hyperthyroidism (Pignon and Mayer 2020).

MATERIALS AND METHODS

A 4-year-old intact female hairless guinea pig was presented to the clinic. According to the owner, the appetite and the faecal output were normal, but the guinea pig was losing weight and was drinking more water than before. Normally the weight was around 860 g, but had now dropped to 778 g. Upon physical examination, the animal was in a medium-to-poor condition and showcased decreased activity and mobility. Skin lesions were present, and the skin was thin and less elastic than normal (Fig. 1). The ears were red and pododermatitis was present on the hind legs. The specimen seemed less muscular, had a large abdomen and was bloated. It was housed alone in a cage, got ad libitum hay and water and the amount of commercial guinea pig feed as indicated on the packaging. Oral vitamin C supplements were administered on a daily basis.

Blood was collected for haematologic and blood biochemistry examinations as well as for measuring cortisol and T4 under isoflurane (Isoflutek, 1,000 mg·g⁻¹ for the production of inhalation vapour liquid, Laboratorios Karizoo) anaesthesia. Radiographic examinations with orthogonal projections were also performed, but other than gas-filled intestines, the results were deemed normal.

Upon assessing the blood results, abdominal ultrasound was performed using a linear 14Mhz and a micro convex

8Mhz probe (Mindray DC 80A X-Insight machine), which showed bilateral adrenal gland hypertrophy. The width of the right adrenal gland was 5.9 mm, and the width of the left gland was 6.5 mm (Fig. 2). The liver was enlarged, with the liver parenchyma showing an increased echogenicity with numerous small, calcified lesions (Fig. 3).

Blood haematology (using a Siemens Advia 2120i Hematology System) showed elevation in heterophil granulocytes (61 %, reference: 22–48 %) in large unstained cells (4.5%, reference $\leq 4.0\%$) and reticulocytes (2.2 %, reference ≤ 1.0 %) and a decrease in lymphocyte numbers (29.1 %, reference: 39–72 %). Heterophile segment percentage was 63 % (reference 22–48 %), monocyte % was 6 (reference < 1.0 %) and small lymphocytes were 22 % (reference 39–72 %).

Blood biochemistry (using a Beckman Coulter AU480 Chemistry Analyzer) showed elevated ALT: 63 U·L⁻¹ (reference: 0–61 U·L⁻¹); GLDH: 23.2 U·L⁻¹ (reference: 0–17 U·L⁻¹); AST: 101 U/L (reference: 25–70, 0–90 U·L⁻¹ and urea: 6.8 mmol·L⁻¹ (reference: 1.5–5.2 mmol·L⁻¹) levels and a lowering of creatinine: 44 $\mu\text{mol}\cdot\text{L}^{-1}$ (reference: 53–195 $\mu\text{mol}\cdot\text{L}^{-1}$). Glucose was 5.8 mmol·L⁻¹. Hormones were measured using a Siemens IMMULITE 2000 Xpi Immunoassay System. The cortisol level was $> 1,380 \text{ nmol}\cdot\text{L}^{-1}$, and T4 was 39.5 nmol·L⁻¹, which is in the normal range (reference: 14–67 nmol·L⁻¹). The reference values were provided by the laboratory where the blood samples were processed. The patient was thus referred to the authors for further investigation and treatment.

The authors opted to perform a modified LDDST to confirm hypercortisolism in the patient. Saliva sampling using the method of Fenske (1996) was tried, but it resulted in an inadequate amount of saliva for the measurements, even when keeping the q-bud in the cheek pouch for over 5 min, as the animal either chewed it off or was extremely stressed from being held. Subsequently, food and water were withdrawn from the animal before sample collection, and the animal was left to calm down for 15 min after the failed previous attempt. Before collection, its preferred pellet feed was shown and rattled in front of the guinea pig, and while the animal was distracted and trying to get to the food presented, a 1 mL syringe was inserted into the mouth and saliva sucked out. After initial saliva sample collection, 0.01 mg·kg⁻¹ dexamethasone (Dexadreson 2 mg·mL⁻¹ injection A.U.V., Intervet International B.V.) was given intramuscularly after diluting it with 0.9% NaCl (Salsol solution for infusion, TEVA Pharmaceuticals). Saliva was collected to determine cortisol levels upon 2, 4 and 8 h after dexamethasone application. Hay and water, but no pellets were offered in between sample collections and were only taken away 30 min before every sample collection to have a clear mouth.

Salivary samples were centrifuged at 3,000 rpm for 5 min in order to separate clear saliva from macroscopic contaminants. Cortisol measurement was carried out from the supernatant using a Siemens IMMULITE 2000 Xpi cortisol immunoassay according to the manufacturer's recommendation.



Fig. 1. Skin lesions were present upon presentation, with the skin being thin and less elastic than normal

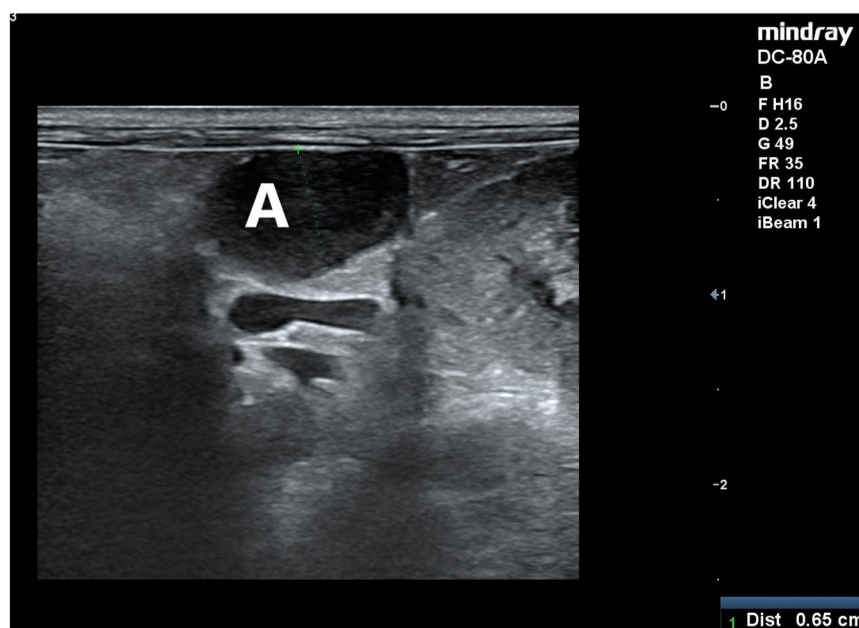


Fig. 2. The left adrenal gland (A) was 6.5 mm on this ultrasonographic image, indicating adrenal gland hypertrophy

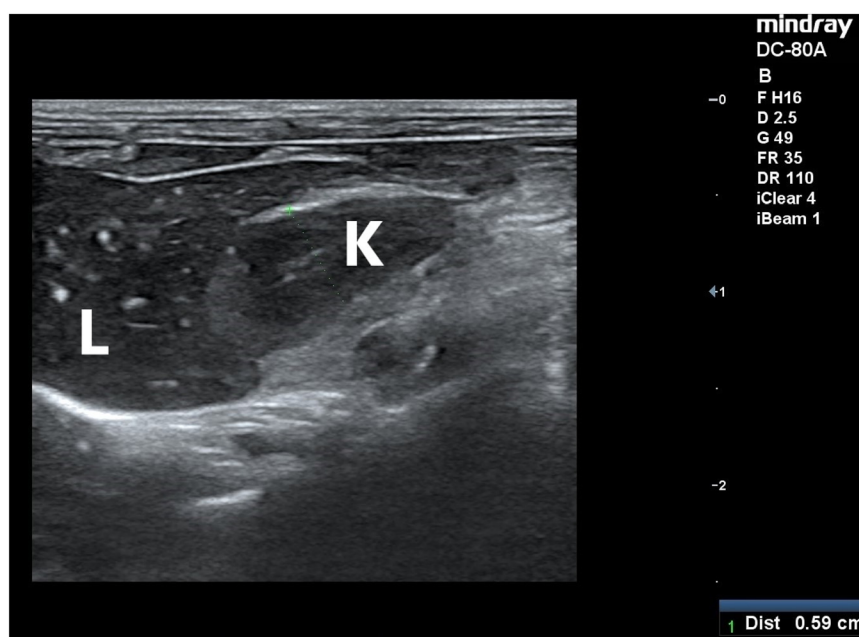


Fig. 3. Ultrasound showed an enlarged liver (L), while the liver parenchyma had numerous small, calcified lesions. The right kidney (K) was also visible, located next to the liver lobe

Spontaneously released urine was also collected before the application of dexamethasone and sent in for further testing. Laboratory testing using a refractometer showed specific gravity to be $1,030 \text{ g}^* \text{L}^{-1}$, and the pH was 8. No blood/haemoglobin, bilirubin, urobilinogen, ketones, nitrite, glucose, proteins, red or white blood cells, bladder or renal epithelial cells or crystals were present upon examination of the urine, but it was contaminated with bacteria.

Urine cortisol was $>1,380 \text{ nmol}^* \text{L}^{-1}$ and urine creatinine was $2,965 \mu\text{mol}^* \text{L}^{-1}$, and UCCR was above 465.4×10^{-6} .

Before applying dexamethasone, the cortisol level was $171 \text{ nmol}^* \text{L}^{-1}$. Two hours after initial application it was $79 \text{ nmol}^* \text{L}^{-1}$, at 4 h it was $70 \text{ nmol}^* \text{L}^{-1}$, and at 8 h it rose to $1,280 \text{ nmol}^* \text{L}^{-1}$.

The animal was subscribed a daily oral dose of $2.5 \text{ mg}^* \text{kg}^{-1}$ trilostane (Vetoryl 5 mg capsule; Dechra Regulatory B.V.) and sent home under the owner's supervision. The owner was also told to syringe feed the animal if it kept losing weight and to increase the vitamin C supplementation to $35 \text{ mg}^* \text{kg}^{-1}$ per day. Silymarin (Hepato Support, RX

Vitamins Inc. Elmsford, USA) was also prescribed for a month as liver enzyme values were mildly elevated. After four weeks the guinea pig was still losing weight and the weight decreased to 676 g. The dose of trilostane was raised to $4 \text{ mg} \cdot \text{day}^{-1}$.

Two months after the initial diagnosis the animal arrived for a checkup, where it was observed to be in a good condition, active and weigh 770 g. Saliva was collected using the same method as used initially and the cortisol level was $56.2 \text{ nmol} \cdot \text{L}^{-1}$. A urine sample collected from the carrier was sent in for laboratory testing. Urine specific gravity was $1,012 \text{ g} \cdot \text{L}^{-1}$. Urine cortisol was $>1,380 \text{ nmol} \cdot \text{L}^{-1}$, urine creatinine was $626 \mu\text{mol} \cdot \text{L}^{-1}$, and UCCR was 2204.5×10^{-6} . Blood glucose was $6.7 \text{ mmol} \cdot \text{L}^{-1}$.

RESULTS

The authors received regular updates on the progression of the disease. The weight remained constant at around 800 g. The animal was more active than before the treatment with trilostane. The diameter of the abdomen was smaller than prior to the treatment and the ears were not red anymore. Skin issues on the body improved, but pododermatitis was still present and progressive.

One year after diagnosis, the animal was active and in a good physical condition upon arrival to the clinic. The weight was 770 g. The skin on the body seemed thin and the pododermatitis progressed (Fig. 4). Hard nodules around 1 cm in size appeared on the abdomen, that were neither painful, nor did they bother the animal (Fig. 5). These weren't visible on radiography either. The circumference of the abdomen decreased further and was 21 cm compared to the 27 cm when treatment had started. Blood draw was not



Fig. 5. Hard nodules around 1 cm in size appeared on the abdomen one year after diagnosis. They were neither painful, nor did they bother the animal

possible on the awake animal, but pin prick blood glucose was $5.7 \text{ mmol} \cdot \text{L}^{-1}$. Ultrasonography showed no changes compared to the previous year. Saliva collection for the



Fig. 4. One year after diagnosis progressing pododermatitis can be seen on the back feet of the guinea pig

measurement of cortisol was attempted, but even though feed was taken away, the guinea pig kept eating its own caecotrophs as soon as they passed, and the mouth was constantly full of faeces. The authors aborted saliva collection in the awake animal after half an hour, as measurements were unlikely to reflect the actual cortisol values. Sample collection under anaesthesia was declined by the owner. Fifteen months after initial diagnosis the animal rapidly started showing signs of retching after medication was given. The animal was presented to a clinic and was subsequently euthanized. The authors were notified 10 days later that unfortunately no post-mortem had been performed.

DISCUSSION

Clinical signs observed in the few cases reported were bilaterally symmetric, nonpruritic alopecia, thin skin, polyuria, polydipsia, bilateral exophthalmos and muscle weakness. The described cases were in middle aged or old animals (Künzel and Mayer 2015; Hocker et al., 2017; Pignon and Mayer, 2020). Symmetric alopecia could not be determined in this case as the patient was a naked guinea pig. The skin is thick and fixed in a healthy guinea pig (Nógrádi et al., 2022), however, thin skin, skin lesions, abrasions and seborrheic changes pathognomic for hypercortisolism were seen on the body of this individual. After the initiation of trilostane treatment these did improve. Hard lumps in the dermis and subcutis of the abdomen could also be palpated which could have been calcinosis cutis, but did not show on radiography. Polydipsia was also an initial complaint of the owner, which is characteristic for hypercortisolism. The animal didn't show signs of exophthalmos as a form of muscle weakness, but a decrease in abdominal muscles was observed, and the guinea pig developed a pot belly with an abdominal circumference of 27 cm. After one year of treatment the latter decreased to 21 cm. Hepatomegaly, which is commonly seen in dogs, was also present in this individual. The age of the animal and the inactivity were also consistent with the literature. The guinea pig was over 5 years old at the last check-up. In the authors' experience, hairless guinea pigs tend to have more health issues and live for a shorter period of time, so an over 1-year survival with hypercortisolism was a satisfactory result.

Radiography didn't help the diagnosis, but ultrasonography showed adrenal hyperplasia, hepatomegaly and calcification of the liver and was the imaging technique of choice to monitor the progression of the disease. The presented case was most likely pituitary-dependent, as both adrenal glands were enlarged on ultrasonographic evaluations undertaken a year apart and the animal responded well to trilostane.

Fenske (1997) applied q-buds into the oral cavity for 5 min, but the authors failed to obtain saliva with this method. Deprivation of preferred feed and the shaking of the bag of pellets yielded results as it both distracted the animal from the fact that a 1 mL syringe was inserted into the oral cavity and also probably enhanced salivation.

Surgical excision of unilateral adrenal tumours has been described in guinea pigs (Hocker et al., 2017). As this guinea pig had bilateral adrenal enlargement, adrenalectomy was not an option for treatment.

The choice for medical treatment of pituitary-dependent hypercortisolism in guinea pigs is trilostane (Kudsk et al., 1983; Pignon and Mayer 2020). It has been given at a dose as high as $4 \text{ mg} \cdot \text{kg}^{-1}$ twice daily, but it can have adverse effects such as inappetence and weight loss (Kudsk et al., 1983; Zaheer and Beaufrère 2020). The authors had to increase the dose one month after diagnosis, and the animal responded well. No inappetence was seen and the animal roughly maintained its weight.

Blood collection in guinea pigs can be difficult. Large volumes can be challenging to collect in awake animals whilst anaesthesia has its risks. Holding a prey species for an awake blood collection will increase cortisol levels. This guinea pig was anaesthetised for the first general blood test. However, this was declined for future samples and, due to the fidgeting nature of the animal, sampling was not possible when it was awake. Stress leukograms are commonly seen in hypercortisolism in dogs (Nelson 2009; Melián 2010). Blood haematology showed signs of a guinea pig stress leukogram as heterophils were elevated and lymphocytes were decreased. Canines with hypercortisolism also commonly show elevated ALT levels (Nelson 2009; Melián 2010). ALT is not sensitive and not specific for hepatocellular damage in guinea pigs (Siegel and Walton 2020). GLDH is sensitive for liver enzymes and, together with AST, are the liver screening parameters of choice in this species (Hein and Hartmann 2005). All three above mentioned blood biochemistry parameters were elevated in this guinea pig. Creatinine was mildly elevated and urea was mildly decreased. The symptoms of polydipsia, weight loss, inactivity and the age of the animal could have been signs of renal disease, but the minimal deviation from normal renal blood biochemistry values, other symptoms inconsistent with renal disease, the diagnosis of hypercortisolism and no renal changes observed on the ultrasound, all suggested that renal disease was not the disease causing the symptoms. A control blood draw for comparison would have been of help in this case. Diabetes mellitus was ruled out as the animal did not have elevated glucose levels at any of the veterinary visits.

Urine was collected from the patient upon arrival and examined twice two months apart. The owner was unable to obtain urine at home which would have reflected the exact condition of the animal in a non-stressful environment. High levels of cortisol can cause urinary infections, and bacteria were seen in the urine of the animal, but this was a free catch sample and no symptoms indicated urinary disease. Thus, microbial sampling was not carried out. Urine specific gravity using a refractometer showed isosthenuria in this guinea pig, which is commonly seen in dogs with hypercortisolism. Urine cortisol levels remained high and could not be determined exactly, but urine creatinine levels decreased between measurements. Due to this UCCR increased. UCCR alone is not diagnostic of hypercortisolism in dogs. There are no current guidelines

for guinea pigs, but the authors do think interpretation used in canines can roughly be transferred to this species and these results were highly suggestive of hypercortisolism.

The saliva cortisol level, just like in canines, showed no suppression after 8 h of applying dexamethasone in the guinea pig, and the steep increase in cortisol levels was also noted, so there appears to be a similarity between the two species. When compared to the measurements at hour 8, the level of cortisol before dexamethasone application seems relatively low. The authors did wait 15 min after having difficulties applying the method of Fenske to collect saliva samples before attempting a method of their own, but that might not have been enough time and the saliva sample might have been diluted.

There are several diseases with similar symptoms to hypercortisolism. Non-pruritic alopecia can be caused by various diseases. Vitamin C deficiency can cause adrenal hypertrophy and an increase in cortisol levels (Enwonwu et al., 1995). Guinea pigs can't synthesise vitamin C, so its role in steroidogenesis has to be taken into account, but in this case, it was ruled out as the animal received adequate daily dietary supplement from the owner. Ovarian cysts are common in guinea pigs, can grow large and cause bilateral alopecia and abdominal distention (Nielsen et al., 2003). The guinea pig was an older intact female, but ovarian cysts were not visible on the ultrasound.

Hyperthyreosis can cause weight loss with normal or increased appetite, hyperactivity or mobility issues, alopecia and PD/PU (Ewringmann and Glöckner 2012), which are similar symptoms to those of hypercortisolism, but it was also ruled out as T4 was in the normal range and no enlarged thyroid glands could be palpated on the ventral neck.

Salivary cortisol levels showed significant increase when animals were isolated, housed with new companions or after car rides (Fenske 1997; Nemeth et al., 2016; Henessy et al., 2000). This animal was housed away from unknown guinea pigs and was given time to relax and settle after its journey to the clinic.

One important finding of this paper is that for non-invasive measurements of cortisol saliva can be collected not just with cotton buds as described by Fenske (1997), but also by using a 1 mL syringe. The most important finding of this study is that the LDDST used in canine medicine to diagnose hypercortisolism can be adapted to guinea pigs and yields results to diagnose Cushing's syndrome in this species. As dexamethasone is more accessible, cheaper and more sensitive than the ACTH stimulation test, it should be a preferred choice from all aspects.

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