Isolated hypoaldosteronism managed by DOCP in a dog with chronic kidney disease and hypercortisolism

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Funding information Research institute for veterinary science of college of veterinary medicine, Seoul National University

Abstract
A 13-year-old spayed female Schnauzer dog with chronic kidney disease (CKD; International Renal Interest Society stage 2, non-proteinuric, normotensive), diabetes mellitus, hypercortisolism and myxomatous mitral valve degeneration (American College of Veterinary Internal Medicine stage B2) presented with electrolyte imbalance that had progressed to hyperkalaemia and hyponatremia, with a sodium to potassium (Na:K) ratio of 19.6. Cortisol levels after the adrenocorticotropic hormone stimulation test were within the therapeutic range, but aldosterone levels were below the reference range; hence, isolated hypoaldosteronism was diagnosed. After administration of deoxycorticosterone pivalate (DOCP), the electrolyte imbalance improved with a Na:K ratio of 27.7. This is the first report of the management of isolated hypoaldosteronism and hypercortisolism using trilostane and DOCP in a dog. This case highlights the importance of recognizing isolated hypoaldosteronism after long-term treatment with trilostane in a canine patient with CKD.

KEYWORDS chronic kidney disease, deoxycorticosterone pivalate, dog, hypoaldosteronism, trilostane

1 INTRODUCTION
Trilostane is a reversible, competitive inhibitor of the adrenocortical enzyme 3β-hydroxysteroid dehydrogenase (Ramsey, 2010). This inhibition blocks the conversion of pregnenolone to progesterone, thereby inhibiting the production of glucocorticoids and, to a lesser extent, mineralocorticoids and sex hormones (Lemetayer & Blois, 2018). Hypoadrenocorticism, with glucocorticoid and mineralocorticoid deficiency, has been frequently reported after trilostane treatment (King & Morton, 2017), but isolated hypoaldosteronism in dogs has rarely been reported (Klein & Peterson, 2010).

Aldosterone is the main mineralocorticoid steroid hormone produced by the zona glomerulosa of the adrenal cortex in the adrenal gland upon stimulation with renin (Booth et al., 2002). Hypoadrenocorticism is a condition marked by decreased synthesis or diminished release of aldosterone from the zona glomerulosa, or resistance to its action on target tissue. When renin levels decrease due to renal injury, the aldosterone levels also decrease, resulting in hyperkalaemia and a condition known as hyporeninaemic hypoaldosteronism (Defronzo, 1980; Kreissler & Langston, 2011). This condition can also be caused by diabetes mellitus (DM), various nephropathies...
or medications such as non-steroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (Rajkumar & Waseem, 2020). Aldosterone deficiency has potentially dangerous consequences such as hyperkalaemia, hyponatremia, severe volume depletion, hypotension and death (White, 2004). Similar to the lack of reports regarding isolated hypoaldosteronism in dogs, there are few reports about aldosterone deficiency in dogs due to genetic (Lobetti, 1998) or acquired defects (Beguin et al., 2020). Therefore, further research is needed regarding hypoaldosteronism in dogs.

For this case, considering that trilostane also has the potential to contribute to or exacerbate kidney disease (Smetts et al., 2012) and aldosterone release problems (Reid et al., 2014), we focused on the correlation of trilostane and hypoaldosteronism in a dog with chronic kidney disease (CKD). In addition, we describe a successful treatment approach of adding deoxycorticosterone pivalate (DOCP) for isolated hypoaldosteronism which resulted in the alleviation of clinical signs.

2 CASE PRESENTATION

A 13-year-old spayed female Schnauzer dog with DM, hypercortisolism, myxomatous mitral valve degeneration (American College of Veterinary Internal Medicine stage B2) and CKD presented with lethargy and an electrolyte imbalance that had progressed to hyperkalaemia (K⁺: 6.68 mmol/L, reference range: 3.6–5.5 mmol/L) and hyponatremia (Na⁺: 131.1 mmol/L, reference range: 145.1–152.6 mmol/L). The sodium to potassium ratio was low (Na⁺: 131.1 mmol/L, reference range: 145.1–152.6 mmol/L, K⁺: 5.65 mmol/L). The aldosterone level was measured before and 1 h after ACTH stimulation test (Synacthen; Zygner et al., 2011; King & Morton, 2017; Ramsey et al., 2008), several

99.2 mmol/L; reference range: 113.2–122.9 mmol/L). To evaluate for aldosterone release problems (Reid et al., 2014), we focused on the lack of reports regarding isolated hypoaldosteronism in dogs. Therefore, further research is needed regarding hypoaldosteronism in dogs.

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99.2 mmol/L; reference range: 113.2–122.9 mmol/L). Considering all diagnostic test results, we diagnosed the patient with isolated hypoaldosteronism.

The patient was then administered DOCP (0.5 mg/kg) subcutaneously, and trilostane was reduced again from 1.25 to 1 mg/kg q12h. Initially, the electrolyte level was monitored every 2 weeks. Although the Na⁺ concentration improved, hyponatremia and hyperkalaemia persisted (Na⁺: 135.4 mmol/L; reference range: 145.1–152.6 mmol/L, K⁺: 5.65 mmol/L; reference range: 3.6–5.5 mmol/L, Cl⁻: 103.8 mmol/L; reference range: 113.2–122.9 mmol/L). Therefore, the DOCP dose was increased to 1 mg/kg, and trilostane was reduced again from 1 to 0.7 mg/kg q12h. As of the 9-month follow-up, the patient's Na⁺: K⁺ ratio has been maintained. Even after the reduction of trilostane, the clinical signs associated with hypercortisolism were well managed. Follow-up electrolyte concentrations are shown in Figure 1. Written informed consent for publication of the clinical detail was obtained from the dog's owner.

3 DISCUSSION

Isolated hypoaldosteronism is uncommon in dogs. The present patient had CKD and DM, which can exacerbate chronic renal failure (Sousa et al., 2016). Furthermore, the combination of these factors could lead to hypoaldosteronism. However, blood analysis revealed only mild azotaemia, and there were no other clinical signs of kidney disease such as hypertension or anaemia in the case patient. Given that trilostane can reduce the glomerular filtration rate (Smetts et al., 2012) and affect the renin-alderosterone axis (Galac et al., 2010), its use in patients with renal failure may exacerbate adverse effects on the kidney.

Trilostane is an inhibitor of 3-beta-hydroxysteroid dehydrogenase; therefore, it can inhibit the conversion of 17-OH pregnenolone to 17-OH progesterone which is the precursor of cortisol. Trilostane can also inhibit the conversion of pregnenolone to progesterone which is the precursor of aldosterone (Ouschac et al., 2012). As trilostane suppress not only cortisol but also minorly suppress aldosterone together, trilostane has adverse effects related to aldosterone. For these reasons, trilostane and angiotensin-converting enzyme (ACE) inhibitors should both be used with caution; trilostane potentiates significant inhibition effects of aldosterone (Griebisch et al., 2014; Reid et al., 2014) with other aldosterone suppressors. ACE inhibitors reduce the secretion of aldosterone (Raebel, 2012), and when used in kidney patients, significant hypoaldosteronism may occur, resulting in severe hyperkalaemia. Therefore, caution should be used with ACE inhibitor administration (Bonnet & Thivolet, 1996; Schepkens et al., 2001; Textor et al., 1982). Similarly, trilostane also should be considered as one of the drugs that should be used carefully in kidney patients in patients with other conditions in which aldosterone may be low.

Another possible cause of hypoaldosteronism is adrenal necrosis. Of the reported cases of iatrogenic persistent hypoadrenocorticisim after trilostane treatment in dogs (Chapman et al., 2004; Gojska-Zygner et al., 2011; King & Morton, 2017; Ramsey et al., 2008), several
cases of dogs with hypercortisolism had variable degrees of adrenal cortical necrosis. The mechanism of cell death in the adrenal glands after treatment with trilostane is unknown. However, trilostane or its metabolites may directly lead to necrosis and/or apoptosis (Reusch et al., 2007). Furthermore, necrosis or apoptosis in the adrenal cortex may lead to adrenal insufficiency. In these cases, hypoadrenocorticism was induced by trilostane, and hypocortisolaemia and hypoaldosteronism were both severe (King & Morton, 2017; Ramsey et al., 2008). However, necrosis is not an abrupt occurrence, and there is a possibility that hypoaldosteronism developed due to the progression of partial adrenal necrosis.

A potential marker of aldosterone inhibition, hyperkalaemia, has been documented in dogs receiving trilostane (Perez, 1972; Szylman et al., 1976). Hyponatremia and hyperkalaemia were confirmed in the present case after the administration of trilostane. The ACTH stimulation test did not show hypocortisolism, but confirmed hypoaldosteronism. Aldosterone deficiency is more immediately life-threatening than cortisol deficiency (Zelinka et al., 2009). DOCP is a parenteral long-acting mineralocorticoid with no glucocorticoid activity (Jaffey et al., 2017; Kintzer & Peterson, 1997). Therefore, we administered DOCP to supplement aldosterone in combination with trilostane. Considering that most previous research reported that DOCP showed sufficient

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**FIGURE 1** Changes in electrolyte profile after trilostane and deoxycorticosterone pivalate (DOCP) treatment. Arrowheads indicate the time of DOCP administration, blue arrow (DOCP, 0.5 mg/kg), red arrow (DOCP, 1 mg/kg) (a). Concentration of blood sodium ion (a), potassium ion (b), Na:K ratio (c), dose of trilostane (d).
effects even at low dosages, this case was an unusual case and the aldosterone level was not significantly low. Therefore, as suggested by several studies, we decided to start with a lower dosage and gradually increase if needed (Bates et al., 2013; Sieberá Ruckstuhl et al., 2019; Vincent et al., 2021). After the injection of DOCP, Na⁺ and K⁺ levels returned to normal. The clinical signs of hypoaldosteronism in the patient also disappeared after this therapy.

4 | CONCLUSION

This case highlights the importance of recognizing isolated hypoaldosteronism after long-term treatment with trilostane in a CKD canine patient with hypercortisolism. In cases of isolated hypoaldosteronism, management with DOCP and continuous monitoring can lead to good outcomes.

AUTHOR CONTRIBUTIONS

Conceptualization, writing-original draft, and writing-review & editing: Su-Min Park. Writing-original draft, visualization, and writing-review & editing: Ju-Hyun An. Investigation: Na-Hyeong Kim. Conceptualization and visualization: Ye-In Oh. Supervision: Kyeong-Won Seo. Conceptualization, supervision, and writing-review & editing: Hwa-Young Youn.

ACKNOWLEDGEMENTS

This study was partially supported by the Research institute for veterinary science of college of veterinary medicine, Seoul National University.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Authors will be required to confirm their adherence to Veterinary Medicine and Science’s Ethics Policy during the submission process. If the manuscript goes on to be accepted, to verify compliance with the above policies, authors must provide an Ethics Statement detailing the ethical review committee approval process and the international, national, and/or institutional guidelines for humane animal treatment followed. If no ethical approval was required, for example, if the paper is a review which includes no original research data.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.954.

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How to cite this article: Park, S.-M., An, J.-H., Kim, N.-H., Oh, Y.-I., Seo, K.-W., & Yoon, H.-Y. (2022). Isolated hypoaldosteronism managed by DOCP in a dog with chronic kidney disease and hypercortisolism. Veterinary Medicine and Science, 8, 2292–2296. https://doi.org/10.1002/vms3.954