PAPER

Hydrocortisone in the management of acute hypoadrenocorticism in dogs: a retrospective series of 30 cases

E. Gunn[1], R. E. Shiel and C. T. Mooney

Small Animal Clinical Studies, School of Veterinary Medicine, University College Dublin, Belfield, Dublin, 4, Ireland

[1]Corresponding author email: eilidh.gunn@ucd.ie

Objectives: The objectives of this study were to describe the efficacy, outcome and adverse effects of intravenous hydrocortisone and fluid therapy for the management of acute hypoadrenocorticism in dogs.

Methods: A retrospective review of dogs with primary hypoadrenocorticism receiving intravenous hydrocortisone and fluid therapy was performed.

Results: Thirty newly-diagnosed dogs were included. There was an excellent clinical response, with all dogs surviving to discharge within a median of 2 days. In 23 cases with complete data, the mean rate of change of sodium over 24 hours was 0·48 (±0·28) mmol/L/hour, while the mean rate of change of potassium was −0·12 (±0·06) mmol/L/hour. Circulating potassium concentration normalised in 68·4% and 100% of cases of by 12 and 24 hours, respectively. Additional treatment for hyperkalaemia was not found necessary. Plasma sodium concentration increased by >12 mmol/L/24 hours on 7 of 23 (30·4%) occasions. One dog exhibited associated temporary neurological signs.

Clinical Significance: Intravenous hydrocortisone infusion and fluid therapy for the management of acute hypoadrenocorticism is associated with a rapid resolution of hyperkalaemia and is well tolerated with few adverse effects. Regular electrolyte monitoring is required to ensure that rapid increases in sodium concentration are avoided.

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INTRODUCTION

Hypoadrenocorticism is a well-recognised endocrine disorder of dogs characterised by deficient mineralocorticoid and/or glucocorticoid production. It can arise as a result of adrenocorticotropic hormone (ACTH) deficiency but is primarily a disorder of adrenal gland dysfunction. It is usually considered to be an immune-mediated disorder, with lymphocytic infiltration progressing to adrenocortical atrophy that typically results in both cortisol and aldosterone deficiency (Addison's disease) (Frank *et al.* 2013).

Hypoadrenocorticism is relatively uncommon, with an estimated prevalence of between 0·06 and 0·33% (Kelch 1996, Bellumori *et al.* 2013), although there is a higher prevalence in certain breeds and familial lines (Boag & Catchpole 2014). It is an important condition for several reasons. Firstly, there are no pathognomonic features, and a high index of suspicion is required to consider it a possible diagnosis and to test for it before treatment commences (Peterson *et al.* 1996). Secondly, if unrecognised and/or untreated, it is associated with high mortality, yet, treated appropriately and expeditiously, a reasonable outcome is expected with a median survival of 4·7 years (Kintzer & Peterson 1997) or an estimated 5-year survival rate of 59% (Hanson *et al.* 2015).

There is a paucity of information regarding the best options, the expected immediate outcome and any potential adverse effects of acute treatment of hypoadrenocorticism. Treatment is primarily directed at restoring fluid volume, correcting electrolyte abnormalities and providing an immediate source of rapid-acting glucocorticoid. The fluid of choice is 0·9% saline because most affected dogs are hyponatraemic. Usually, high rates of 40 to 80 mL/kg/hour are recommended for the first 1 to 2 hours, gradually decreasing thereafter depending on response, although rates of 90 mL/kg/hour are also used (Burkitt Creedon 2015).

Dexamethasone and prednisolone are the most commonly recommended glucocorticoid drugs, but the doses vary considerably, from as low as 0·1 mg/kg for dexamethasone to as high as 20 mg/kg for prednisolone (Kintzer & Peterson 2014, Scott-Moncrieff 2014, Burkitt Creedon 2015). Using glucocorticoid replacement alone, circulating potassium concentrations decrease through the effects of dilution, improved renal perfusion and enhanced potassium excretion, although how quickly this is achieved is unknown. Other treatments (intravenous insulin and glucose or calcium) may be required to prevent the life-threatening myocardial toxicity associated with severe hyperkalaemia. A potential adverse effect of treatment can result from the rapid correction of hyponatraemia with subsequent development of osmotic demyelination syndrome, which can be fatal, and has been reported in dogs with hypoadrenocorticism and other disorders associated with hyponatraemia (O'Brien *et al.* 1994, Brady *et al.* 1999, Churcher *et al.* 1999, MacMillan 2003).

Hydrocortisone is an alternative drug that is a synthetic analogue of cortisol with equipotent mineralocorticoid and glucocorticoid activity. In experimental studies, a dose of 0·625 mg/kg/hour hydrocortisone sodium succinate intravenously resulted in mean circulating cortisol concentrations exceeding 700 nmol/L (Church *et al.* 1999). Doses of between 0·5 and 0·625 mg/kg/hour have therefore been advocated as providing sufficient glucocorticoid and mineralocorticoid activity to effectively correct acute adrenal hypofunction associated with hyperkalaemia (Church *et al.* 1999, Church 2012). However, there are no studies specifically evaluating the efficacy of any dose of hydrocortisone in the acute management of canine hypoadrenocorticism.

The aim of this study was to retrospectively describe the efficacy, outcome and adverse effects associated with intravenous hydrocortisone and fluid therapy for the acute management of hypoadrenocorticism in dogs.

MATERIALS AND METHODS

Case selection

Case records of dogs with naturally-occurring confirmed primary hypoadrenocorticism being presented to University College Dublin (UCD) Veterinary Hospital were retrospectively reviewed in the period from August 2005 to August 2015. Dogs were included if they had evidence of combined glucocorticoid and mineralocorticoid deficiency, defined as inadequate cortisol production during an ACTH stimulation test, together with compatible electrolyte abnormalities (hyponatraemia or hyperkalaemia or both). In dogs that had been administered glucocorticoids previously, evidence of inadequate aldosterone production was also required. Cases were subsequently excluded if the event was a repeat crisis or if there was evidence of a concurrent disease likely to affect fluid balance or electrolyte concentrations.

Clinicopathological evaluation

Blood samples were obtained by jugular venepuncture and placed in EDTA or lithium heparin tubes for haematological and biochemical analyses, respectively. All analyses were performed at the UCD Veterinary Diagnostic Laboratory within 3 to 4 hours of collection using the Advia 2120 (Siemens Medical Solutions Diagnostics) and the RX Imola (Randox) biochemistry analyser.

Additional electrolyte concentrations measured during treatment were performed using the Rapidpoint 500 (Siemens Medical Solutions Diagnostics). Blood samples were collected into lithium heparin tubes or pre-heparinised syringes and analysed within 10 minutes of venepuncture.

ACTH stimulation tests were performed in a standardised manner. Cortisol concentrations were measured before and 1 hour after tetracosactide (Synacthen, Alliance or Tetracosactide Solution for Injection, Dechra, depending on availability) administration using a chemiluminescent assay (Immulite 1000 (up to 2012) or 2000 (from 2012), Siemens Medical Solutions Diagnostics). Tetracosactide was given at a dose of 250 ug for dogs >5 kg and 125 ug for dogs <5 kg or at 5 ug/kg. Pre- and post-ACTH aldosterone concentrations were measured by a validated radioimmunoassay at Nationwide Specialist Laboratories, UK.

Treatment protocol

Each dog received a dose of 0·5 or 0·625 mg/kg/hour hydrocortisone sodium succinate (Solu-cortef, Pfizer) intravenously according to the standard hospital protocol. This protocol dictated that 0·9% saline be used at an initial intravenous rate of no more than 7·5 to 10 mL/kg/hour for the first 1 to 2 hours, decreasing to approximately 5 mL/kg/hour thereafter. Adjustment of this rate was at the clinician's preference, but caution was advised in using higher rates unless specifically indicated. In dogs with significant hypoglycaemia, dextrose was added to 0·9% saline as required. During treatment, alternative fluids could be used if deemed necessary.

Dogs were discharged once oral therapy [fludrocortisone acetate (Florinef, Bristol-Myers Squibb) and prednisolone] had commenced, intravenous fluid therapy had ceased and the animal was eating satisfactorily.

Data analyses

Continuous data were tested for normality using the Shapiro-Wilk method (GraphPad Prism, GraphPad Software Incorporated). Non-parametric data were reported as median (interquartile range), while parametric data were reported as mean [± standard deviation (sd)]. Linear regression was used to evaluate the relationships between sodium and potassium concentrations at the onset of hydrocortisone treatment (independent variables) and average hourly rates of change of sodium and potassium concentration over the initial 24 hours of treatment (dependent variables), respectively.

RESULTS

In total, 34 case records were identified. Two were excluded for concurrent diseases (severe pancreatitis and unstable diabetes mellitus) and 2 because they were long-standing cases and referred for management of a repeat crisis. Thus, 30 newly diagnosed dogs were included, including 2 that had had blood samples and

an ACTH stimulation test performed at their primary veterinary practice with immediate referral for treatment.

The dogs comprised 26 (86·7%) pedigree animals, including cocker spaniels (n=6), 2 each of Jack Russell terrier, cavalier King Charles spaniel and West Highland white terrier and one each of standard poodle, Labrador retriever, samoyed, Border collie, Skye, Scottish, Cairn and Yorkshire terrier, rottweiler, Weimaraner, standard dachshund, English springer spaniel, Rhodesian ridgeback, and bichon frise. The remaining 4 (13·3%) dogs were cross-breeds of which 2 were labradoodles and 1 was a West Highland white terrier–bichon frise cross. There were 18 (60·0%) females (14 neutered, 4 entire) and 12 males (7 neutered, 5 entire). The median age at the time of diagnosis was 4 years (range 0·3 to 9·0 years).

Routine clinicopathological data for the cases presenting for both initial diagnosis and treatment are summarised in Table 1. In all but 2 cases, the pre- and post-ACTH cortisol concentrations were <27·59 nmol/L. In the remaining 2 cases, the pre cortisol concentrations of 30·8 and 29·8 nmol/L increased to 30·6 nmol/L and 42·6 nmol/L, respectively. Pre- and post-ACTH aldosterone concentrations were measured in 13 cases and were <20 pmol/L and <20 pmol/L, respectively, in all cases (reference interval; pre <960 pmol/L, post-ACTH 200 to 2100 pmol/L).

All dogs received intravenous fluid therapy for a period of time prior to hydrocortisone infusion, at least while the ACTH stimulation test was performed. Nevertheless, all dogs remained hyperkalaemic or hyponatraemic or both immediately prior to commencing hydrocortisone treatment at a dose of 0·5 mg/kg/hour (n=9) or 0·625 mg/kg/hour (n=21). Of these treatment events, there was insufficient electrolyte monitoring to fully assess the rate of change in sodium and potassium concentrations in 7 cases. In the remaining 23 cases, over the initial 24 hours of treatment, the mean rate of change of sodium concentration was 0·48 (±0·28) mmol/L/hour while that of potassium concentration was −0·12 (±0·06) mmol/L/hour. The results for each individual event are illustrated in Figs 1 and 2. Sodium and potassium concentrations at onset of hydrocortisone treatment were predictive of the average hourly rate of change of the concentration of each parameter over the initial 24 hours of treatment ($Y=-0{\cdot}02251*X+3{\cdot}335$, $R^2=0{\cdot}571$, $P<0{\cdot}0001$; $Y=-0{\cdot}04136*X+0{\cdot}1333$, $R^2=0{\cdot}6072$, $P<0{\cdot}0001$, respectively) (Figs 3 and 4). On 18 of these occasions, there was hyperkalaemia at the start of the hydrocortisone infusion, and the potassium concentration had normalised in 12 (66.7%) cases by 12 hours and in all (100%) cases by 24 hours.

All of the dogs survived to discharge. The median time from the start of hydrocortisone infusion until discharge was 2 (range: 2 to 4) days. There was a dramatic clinical improvement in all animals. Overall, the treatment was well tolerated, with adverse effects only noted in 1 of the 30 (3·3%) dogs. In this dog, there was an increase in sodium concentration of 14·5 mmol/L over 14·3 hours, and this was presumed to account for the clinical signs of ataxia, delayed conscious proprioception, difficulty prehending food and mental dullness that developed. These signs were transient, and a repeat neurological examination 1 week later revealed a dramatic improvement with only mild dysphagia persisting. Including this dog, on 7 of the 23 (30·4%) occasions when it could be calculated, the sodium concentration increased by more than 12 mmol/L in 24 hours (Table 2). In these dogs, a combination of decreasing (n=1) or discontinuing the hydrocortisone infusion (n=6), and discontinuing or decreasing the fluid rate (n=3) or switching fluid type (0.45% saline/5% dextrose free water (n=3) or compound sodium lactate (n=1)) was employed to decrease the rate of sodium increase.

DISCUSSION

The dogs included in this case series represent typical examples of primary hypoadrenocorticism. The median age was 4 years, similar to the median age range of 2·5 to 5·0 years reported in other large case series (Melián & Peterson 1996, Peterson *et al.* 1996, Adler *et al.* 2007, Baumstark *et al.* 2014). As in these previous reports, the majority were female and purebred. In total,

Table 1. Clinicopathological data from dogs with primary hypoadrenocorticism presenting for initial diagnosis and treatment

	Parameter	Number of dogs	Number of dogs with abnormal values		Range	Reference interval
			Above	Below		
CBC	Haematocrit	27	3 (11·1%)	7 (25·9%)	0·12 to 0·63	0·37 to 0·55 L/L
	Lymphocyte count	27	7 (25·9%)	2 (7·4%)	0·85 to 7·92	1 to 3·6 x10^9/L
	Eosinophil count	27	1 (3·7%)	0	0 to 2·81	0 to 1·47 x10^9/L
Biochemistry	Urea	27	18 (66·7%)	0	4·8 to 54·4	3·6 to 8·6 mmol/L
	Creatinine	27	16 (59·3%)	0	52 to 359	20 to 120 umol/L
	Phosphorous	27	15 (55·6%)	0	1·33 to 4·32	0·8 to 1·8 mmol/L
	Total Calcium	27	10 (37·0%)	2 (7·4%)	1·94 to 4·3	2·3 to 3·0 mmol/L
	Albumin	27	8 (29·6%)	2 (7·4%)	22 to 45·5	25 to 38 g/L
	Cholesterol	27	7 (25·9%)	6 (22·2%)	1·42 to 9·21	3·2 to 6·5 mmol/L
Electrolytes	Sodium	27	0	23 (85·1%)	108·5 to 140·6	137 to 151 mmol/L
	Potassium	27	16 (59·2%)	0	4·27 to 8·19	3·7 to 5·8 mmol/L
	Chloride	27	0	22 (81·5%)	80·4 to 113·4	99 to 110 mmol/L
	Ionised Calcium	25	4 (16·0%)	3 (12·0%)	1·14 to 1·82	1·2 to 1·4 mmol/L
Blood Gas	pH	25	1 (4·0%)	12 (48·0%)	7·18 to 7·45	7·35 to 7·44
	Bicarbonate	25	1 (4·0%)	18 (72·0%)	9·3 to 24·9	20·8 to 24·4 mmol/L
	pCO_2	25	3 (12·0%)	14 (56·0%)	3·46 to 6·03	4·47 to 5·48 kPa

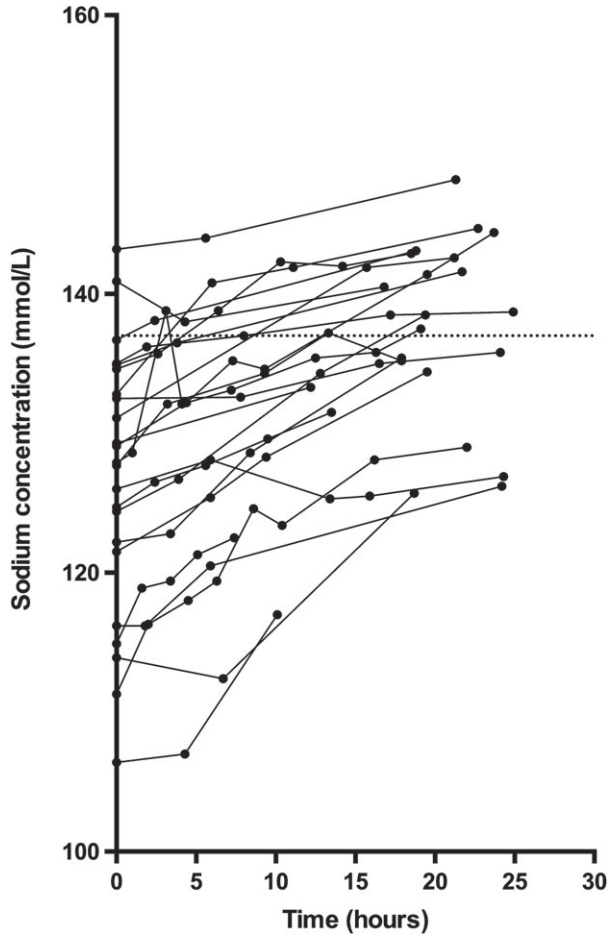

FIG 1. Change in sodium concentration over the initial 24 hours of treatment. The dotted line indicates the lower limit of the reference interval (137 mmol/L)

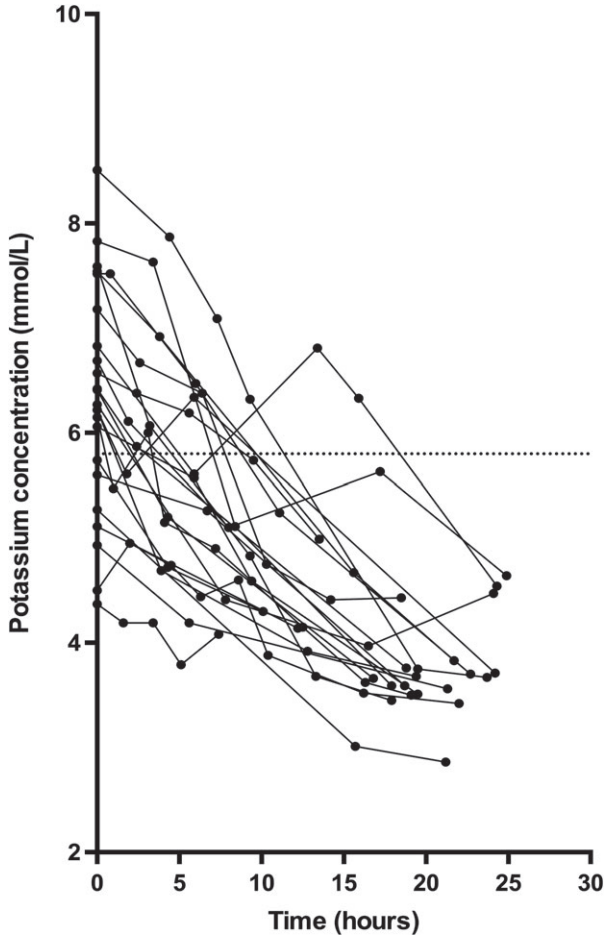

FIG 2. Change in potassium concentration over the initial 24 hours of treatment. The dotted line indicates the upper limit of the reference interval (5·8 mmol/L)

18 different pedigree breeds were represented, including the standard poodle, Jack Russell terrier, English springer spaniel, West Highland white terrier and cocker spaniel for which genetic susceptibility and putative candidate genes have been recognised (Famula *et al*. 2003, Short *et al*. 2013, 2014). Interestingly, of the 4 cross-breeds represented, 3 were either poodle or West Highland white terrier crosses. The clinicopathological abnormalities noted reflect those reported previously, with the majority being azotaemic and hyperphosphataemic with concurrent hypochloraemia, hyponatraemia and hyperkalaemia and both acidosis and hypobicarbonaemia (Peterson *et al*. 1996, Adler *et al*. 2007) with a few exhibiting hypercalcaemia (Peterson & Feinman 1982, Adler *et al*. 2007, Adamantos & Boag 2008). Lymphocytosis was observed more and eosinophilia less frequently than reported previously (Peterson *et al*. 1996). However, the importance of lymphocyte and eosinophil counts is that reduced values are unusual in dogs with glucocorticoid deficiency, and the absence of such a change provides as much supportive evidence of hypoadrenocorticism as increased counts (Seth *et al*. 2011, Zeugswetter & Schwendenwein 2014). The haematocrit varied, being both increased and decreased as reported previously (Peterson *et al*. 1996), with significant anaemia being a feature in a few isolated cases presumably related to gastrointestinal haemorrhage as supported by the concurrent hypoalbuminaemia observed.

All the dogs had pre ACTH cortisol concentrations less than 50 nmol/L, above which hypoadrenocorticism is considered unlikely (Lennon *et al*. 2007, Bovens *et al*. 2014). However, values below this cut-off are not specific for hypoadrenocorticism, and the lack of cortisol stimulation following ACTH administration provides more substantive evidence of hypoadrenocorticism. Previous glucocorticoid treatment may interfere with the results of an ACTH stimulation test and, when known or suspected, a diagnosis of hypoadrenocorticism was supported by a lack of aldosterone production as previously described (Willard *et al*. 1987, Baumstark *et al*. 2014). During the course of this study, different doses of ACTH were used because of difficulties with ACTH supply and cost. This is unlikely to have impacted diagnosis as ACTH doses as low as 5 ug/kg, as used herein, have been reported to adequately distinguish dogs with non-adrenal illness and hypoadrenocorticism (Lathan *et al*. 2008).

Repeat events were not included in the assessment of treatment because a single dog's response or a potential effect of previous mineralocorticoid use may have unduly influenced the conclusions drawn from this case series. However, in completing the

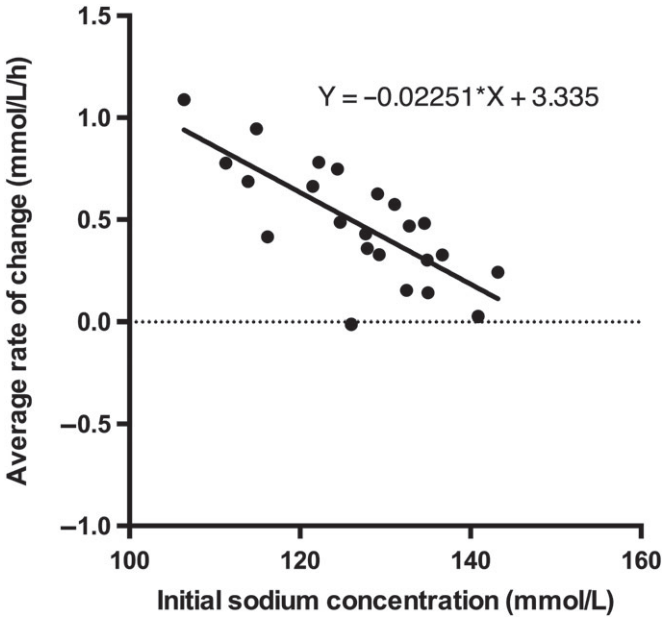

FIG 3. Relationship between sodium concentration at onset of hydrocortisone treatment and average hourly rate of change of sodium concentration over the initial 24 hours of treatment

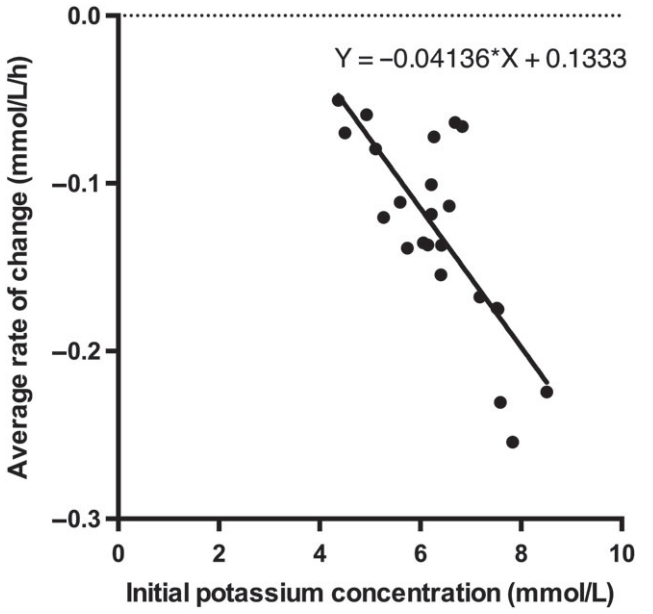

FIG 4. Relationship between potassium concentration at onset of hydrocortisone treatment and average hourly rate of change of potassium concentration over the initial 24 hours of treatment

study, it became clear that repeat crises were not uncommon. The risk of recurrent Addisonian crises is well-recognised, although there is little information available suggesting how likely it is in individual cases. In a study of 205 dogs undergoing treatment for hypoadrenocorticism, only 5 (2·4%) died of acute adrenocortical insufficiency after diagnosis and commencement of medical management, but no mention is made of any other dogs requiring repeat acute management (Kintzer & Peterson 1997). In another study of 297 dogs with hypoadrenocorticism, the cause of death/euthanasia was related to adrenocortical insufficiency in 27%, although whether this is related to repeat crises is unclear (Hanson *et al.* 2015). The likelihood of repeat crises may be an important consideration when owners are reflecting on the impact of life-long therapy.

Table 2. Baseline and final sodium concentration in dogs in which the rate of change of sodium exceeded 12 mmol/L in 24 hours

Baseline sodium concentration (mmol/L)	Final sodium concentration (mmol/L)	Time after HC started hours
106·4	120·9	14·3
129·1	141·4	19·5
124·4	138·5	19·4
111·3	128·1	16·2
121·5	134·4	19·5
122·2	135·4	17·9
114·9	134·1	16·6

HC hydrocortisone sodium succinate

This study demonstrates that intravenous hydrocortisone together with intravenous fluids at conservative rates is reliable and effective in the acute management of hypoadrenocorticism. The potassium concentration decreased rapidly and consistently normalised within 24 hours after commencing therapy. Sodium concentrations generally increased, although caution was required to avoid rapid increases, and as a consequence, the sodium concentration reached the reference interval in only a few animals. All dogs survived to discharge, and the median time to discharge was short at 2 days.

The administration of hydrocortisone for the acute management of hypoadrenocorticism has disadvantages and advantages. On the one hand, it is measured as cortisol, and its administration must be postponed until after the completion of the ACTH stimulation test. On the other hand, it is widely available for human use, relatively inexpensive and has a long shelf-life. Its short half-life means that if administered erroneously prior to a definitive diagnosis of hypoadrenocorticism, it is unlikely to have significant long-term effects. Most importantly, it has equal glucocorticoid and mineralocorticoid activity, and there are several reports that support the doses used in this study. Firstly, cortisol is a known stress hormone, and concentrations increase significantly under the influence of non-adrenal illness and major surgeries (Church *et al.* 1994). Intravenous infusion of hydrocortisone sodium succinate at a dose of 0·625 mg/kg/hour resulted in a detectable increase in circulating cortisol concentrations, with plateau concentrations exceeding 700 nmol/L in both healthy dogs and those with experimentally induced hypoadrenocorticism (Lamb *et al.* 1994, Church *et al.* 1999). High aldosterone concentrations of 3000 to 3500 pmol/L are reported in dogs with hyperkalaemia from non-adrenal causes (Church *et al.* 1999). Given that the relative mineralocorticoid activity of aldosterone is approximately 400 times that of cortisol (Hebel 1997), a continuous infusion of 0·5 to 0·625 mg/kg/hour hydrocortisone sodium succinate has been suggested as providing sufficient glucocorticoid and mineralocorticoid activity to effectively correct acute adrenal hypofunction (Church *et al.* 1999). Although lower doses of approximately 0·3 mg/kg/hour have also

been recommended (Panciera 2012), the requisite high cortisol values may not be achieved (Church *et al*. 1999).

Overall, it is difficult to directly compare this treatment protocol with others. Firstly, there is a relative paucity of data available on the acute management of hypoadrenocorticism. Secondly, there is no agreed consensus on other corticosteroids, and a wide range of doses are reported in standard textbooks. Thirdly, the dose of intravenous fluids varies dramatically from relatively low rates as described in this study to high "shock rates" described elsewhere.

Dexamethasone has a relative glucocorticoid activity approaching 30 times that of hydrocortisone but with no mineralocorticoid activity (Hebel 1997). The most commonly reported intravenous dosages of dexamethasone for hypoadrenocorticism include 0·2 to 0·5 mg/kg once (Plumb 2008); 0·1 to 2·0 mg/kg followed by 0·05 to 0·1 mg/kg every 12 hours (Scott-Moncrieff 2014), 0·5 to 2 mg/kg followed by 0·05 to 0·1 mg/kg every 12 hours (Bovens *et al*. 2014) and 2 to 4 mg/kg every 2 to 6 hours (Kintzer & Peterson 2014). This equates to a dose of 2·67 mg/kg hydrocortisone at the lowest recommended dexamethasone dose (0·1 mg/kg for 12 hours) or 107 mg/kg at the highest dose (4 mg/kg every 2 hours) compared with maximum respective hydrocortisone doses used in this study of 7·5 mg/kg and 1·25 mg/kg over a similar time period (12 and 2 hours, respectively). Thus, it is likely that dexamethasone at almost all but the lowest of the recommended dosages provides a relative excess of glucocorticoid. There is limited evidence that such dexamethasone doses are beneficial, but they could contribute to gastrointestinal haemorrhage and other deleterious glucocorticoid side effects (Panciera 2012).

Prednisolone has a relative glucocorticoid activity of approximately 4 times that of hydrocortisone and 0·8 times its mineralocorticoid activity (Robinson & Verbalis 2011). Like hydrocortisone, its administration must be postponed until after completion of the ACTH stimulation test. The most commonly reported intravenous dosages of prednisolone include 1 to 2 mg/kg followed by 0·5 mg/kg every 6 to 8 hours (Scott-Moncrieff 2014, Burkitt Creedon 2015) and 15 to 20 mg/kg (Melián & Peterson 1996, Kintzer & Peterson 2014). This equates to a dose of approximately 4·0 mg/kg hydrocortisone at the lowest recommended dose (1 mg/kg for 12 hours) or 80 mg/kg at the highest dose (20 mg/kg over 24 hours) compared with maximum respective hydrocortisone doses used in this study of 7·5 mg/kg and 15 mg/kg over a similar time period (12 and 24 hours, respectively). Again, it is likely that prednisolone at any of the recommended dosages provides a relative excess of glucocorticoid.

There are some comparisons that can be made. Firstly, the median hospitalisation time of 2 days with a range up to 8 days equates to a hospitalisation period from 2 to 5 days reported in 38 Addisonian dogs treated with intravenous fluids and either dexamethasone or prednisolone (Melián & Peterson 1996). For such a life-threatening disorder, this short hospitalisation time is remarkable and reflects that a rapid response is achievable. If there is a more delayed response, the diagnosis should be reviewed or an alternate concurrent disorder sought.

Hyperkalaemia is known to be life-threatening in hypoadrenocorticism, and its management is usually achieved using intravenous fluid therapy and glucocorticoids and, where necessary, ancillary treatments such as dextrose and regular insulin, calcium gluconate and sodium bicarbonate (Bovens *et al*. 2014, Kintzer & Peterson 2014, Scott-Moncrieff 2014, Burkitt Creedon 2015). In this study, potassium concentrations normalised with the use of fluid therapy and hydrocortisone alone, and no dog required ancillary treatment for the management of hyperkalaemia. By contrast, of the 38 Addisonian dogs treated with intravenous fluids and dexamethasone or prednisolone reported elsewhere, 6 (17%) required additional insulin and glucose treatment to decrease serum potassium concentrations and correct its associated electrocardiographic abnormalities (Melián & Peterson 1996). Approximately 50% of the dogs in the present study were acidotic on presentation. The use of sodium bicarbonate has been advocated for management of severe metabolic acidosis in hypoadrenocorticism (Kintzer & Peterson 2014). However, it has also been suggested that fluid therapy alone is sufficient to correct acid/base disturbance (Bovens *et al*. 2014, Scott-Moncrieff 2014). Certainly, in the current case series, no dog specifically required bicarbonate therapy for the management of metabolic acidosis.

Only 1 dog in the present study developed any adverse effect potentially related to treatment. This dog developed neurological signs possibly related to osmotic demyelination syndrome as a result of rapid correction of circulating sodium concentrations. Osmotic demyelination has the potential to incur life-threatening consequences, and whilst an unusual complication, it is imperative that clinicians be vigilant in taking measures to prevent its development. It is currently recommended that correction of hyponatraemia should not exceed 10 to 12 mmol/L/day or 0·5 mmol/L/hour (O'Brien *et al*. 1994, Brady *et al*. 1999, Churcher *et al*. 1999, MacMillan 2003). In humans, the risk of development of adverse effects is the highest at the lowest sodium concentrations, but not all patients in whom sodium is rapidly corrected develop associated clinical signs (Robinson & Verbalis 2011). Similarly, the dog that developed clinical signs had the lowest sodium of all 7 dogs exhibiting a rapid increase in sodium concentration (>12 mmol/L/hour), but it was the only case that developed such signs. However, it was not the only dog with such a low baseline sodium concentration. Interestingly, this study demonstrated that the rate of change in potassium and sodium were correlated to baseline concentrations: the higher the potassium concentration the more rapidly it decreased, and the lower the sodium the more rapidly it increased. The reasons for this are unclear, and it may not be solely related to hydrocortisone treatment but a risk of other treatments for hypoadrenocorticism. Certainly, the non-osmotic stimulus for vasopressin release is abolished with volume repletion, thus permitting the renal excretion of solute-free water, which in itself will contribute to the correction of hyponatraemia (DiBartola 2012). In practical terms, the changes described mean that, irrespective of baseline potassium concentrations, an excellent response in achieving an appropriate decrease with treatment is likely. On the other hand, sodium concentrations, particularly at low values, are more likely to increase rapidly and carry the greatest risk of inducing osmotic demyelination. Using this treatment protocol, it is the change

in sodium concentration that perhaps requires the greatest attention.

This study has many limitations, not least the small case numbers and retrospective study design but also the dependence on each clinician adhering to the hospital protocol and accurately maintaining the clinical records. Whilst the intravenous fluid rates recommended were conservative, it could not be guaranteed that these rates were strictly followed. There were also varying monitoring times for repeat electrolyte measurement. Such variations are likely to reflect clinical practice where each animal's needs differ and are at the discretion of individual clinician preference. No firm conclusions could be made regarding the relative effects of hydrocortisone or intravenous fluids as all dogs received both.

In conclusion, the use of a hydrocortisone infusion together with intravenous fluid administration represents an effective treatment for dogs presenting with acute hypoadrenocorticism and results in the rapid control of hyperkalaemia. Too great an increase in sodium concentration is a possibility, particularly at low starting values, and care should be taken to avoid its development. Further research is required to further define this treatment, especially in comparison to possible outcomes of other treatment options.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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