Developments in treatment of hypoadrenocorticism

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Once a diagnosis of hypoadrenocorticism has been made – which, in itself, can be a challenge – the question remains of how to manage it.

Some notable changes have been made in the approach to the acute and chronic treatment of the disease; particularly after the launch of desoxycorticosterone pivalate (DOCP) in the UK. This article focuses on developments in this area with the aim to better refine our control of the disease.

Acute management

Emergency treatment of dogs with suspected hypoadrenocorticism involves managing electrolyte derangements, hypovolaemia and other potential complications, such as hypoglycaemia.

Fluid therapy

Traditionally, the fluid therapy of choice was 0.9% NaCl given at shock rates to effect. This can be acidifying, which can be detrimental in patients with hypoadrenocorticism as they typically present with metabolic acidosis. In addition, correction of metabolic acidosis also promotes intracellular movement of potassium.

In a study of cats with experimentally induced urethral obstruction resulting in the development of metabolic acidosis and hyperkalaemia, 0.9% NaCl was compared to lactated Ringer’s solution. Lactated Ringer’s solution was more efficient in restoring the acid base and electrolyte balance. Concern exists that increasing the sodium concentration rapidly in patients with chronic hyponatraemia can result in complications such as central pontine myelinosis.

It is recommended the correction of hyponatraemia should not exceed 10mmol/L/day to 12mmol/L/day to prevent this condition. Because of these disadvantages, it is increasingly recommended a buffered isotonic crystalloid solution containing low concentrations of potassium, such as Hartmann’s solution, should be considered.

Glucocorticoid and mineralocorticoid replacement

Various options are available for glucocorticoid and mineralocorticoid replacement, dependent on
availability and the patient’s requirement.

In very unstable patients requiring immediate therapy, dexamethasone is the treatment of choice as it can be administered alongside performing the adrenocorticotropic hormone (ACTH) stimulation test, because it is one of the only steroids that does not cross react with most cortisol assays. The disadvantage of dexamethasone is that the glucocorticoid activity is markedly higher than the mineralocorticoid activity and the reported dose range is wide (0.1mg/kg to 4mg/kg every 2 to 12 hours).

Hydrocortisone is an alternative and short-acting IV treatment. It has equal glucocorticoid and mineralocorticoid activity, which should provide more balanced replacement. Hydrocortisone can be administered as a constant rate infusion (CRI; 0.5mg/kg/hr to 0.625mg/kg/hr) or intermittent IV bolus (2mg/kg to 4mg/kg q four to six hours) to effect and has been shown to rapidly resolve hyperkalaemia in hypoadrenocorticoid dogs with few adverse effects.

The main disadvantage of hydrocortisone is as it is measured as cortisol, it cannot be administered before completion of the ACTH stimulation test. In the author’s experience, in the majority of dogs, treatment with fluid therapy during the short delay while the ACTH stimulation is performed is normally sufficient to stabilise and prevent further deterioration, before administration of hydrocortisone.

**Chronic management**

In the UK, before 2016, fludrocortisone with or without the addition of prednisolone was the treatment of choice for chronic therapy.

In April 2016, a suspension of DOCP was launched and is the first veterinary licensed treatment for hypoadrenocorticism in Europe. This, in combination with a shortage of fludrocortisone in the UK, resulted in a change to DOCP therapy for the majority of dogs. As it is licensed it should be used in all newly diagnosed cases. Dogs already receiving fludrocortisone can also be carefully changed to DCOP.

**DOCP**

DOCP is a parenteral administered long-acting mineralocorticoid alternative. In contrast to fludrocortisone it has no glucocorticoid activity. Therefore, in all cases treated with DOCP additional glucocorticoid therapy (normally prednisolone) is required.

The initial dose of additional prednisolone is 0.2mg/kg to 0.4mg/kg; however, this can be titrated downwards to effect (particularly if signs of iatrogenic hyperadrenocorticism develop) or increased during times of stress/concurrent illness.
The average dose of prednisolone required for long-term management is around 0.2mg/kg/day\textsuperscript{8,9}.

**Starting dose and frequency**

The initial dose of DOCP is 2.2mg/kg SC given once every 25 days\textsuperscript{6}. Most dogs require lower doses long term and less frequent treatment than every 25 days.

As under-dosage can potentially be life threatening, it is still recommended DOCP is administered at this dose with the knowledge most will ultimately require dose reduction. This is to prevent unnecessary crisis events in a small number of patients.

**Monitoring**

It is advised to repeat electrolytes and calculate the Na+/K+ ratio 10 days after the first dose of DOCP is given. Based on this result, the dose of DOCP given at day 25 is calculated\textsuperscript{6}. The electrolytes are also repeated on day 25 prior to repeat DOCP administration.

In some circumstances, dependent on the Na+/K+ ratio and owner/clinician preference, the dose frequency can be increased. Some patients will develop persistent polyuria (PU) and polydipsia (PD) despite reduction of prednisolone to the minimum physiological dose. In these dogs it is possible PU/PD is a result of mineralocorticoid excess, in which case, reducing the dose of DOCP could also be considered – provided the Na+/K+ ratio is not less than 275.

**Changing from fludrocortisone to DOCP**

When transitioning dogs from fludrocortisone to DOCP, it is recommended DOCP is administered before phasing out fludrocortisone over a period of two to three days. In dogs previously only receiving fludrocortisone, it is important to remember to add prednisolone back in to the treatment protocol.

In some patients there may be a preference to continue with fludrocortisone therapy.

**Fludrocortisone dose frequency**

The question remains of what frequency fludrocortisone should be given. In the majority of earlier publications reporting on the use of fludrocortisone in dogs, dose frequency was not recorded\textsuperscript{8,9}. Both once and twice-daily dosing have been suggested\textsuperscript{7,9}.

Evidence suggests the time to stabilisation is not different between dogs started on once daily versus those started on twice-daily fludrocortisone\textsuperscript{10}. The study did find in a small group of dogs that failed to stabilise quickly on once-daily therapy, a change to twice-daily therapy (median six months after starting therapy) resulted in rapid stabilisation.
Therefore, once or twice-daily dosing could be considered initially and is unlikely to affect how quickly dogs will stabilise. However, if a dog on once-daily therapy is not improving then perhaps changing to twice-daily therapy could result in an improvement.

**Fludrocortisone and prednisolone**

After initial diagnosis, all dogs should receive fludrocortisone in combination with prednisolone. However, often the dose of prednisolone can subsequently be reduced (initial dose 0.3mg/kg to 0.36mg/kg, final dose 0.18mg/kg to 0.2mg/kg). Some dogs require higher prednisolone doses for a few days after the initial diagnosis (0.5 mg/kg), especially if they present in acute crisis. Concurrent use of prednisolone, together with fludrocortisone, resulted in faster stabilisation times in dogs10. This would indicate prednisolone should continue until stabilisation has been achieved, then the dose could be carefully titrated (or continued) to effect, dependent on clinical signs (such as appetite, gastrointestinal signs and demeanour).

Some dogs can continue with prednisolone every other day, or fludrocortisone therapy alone, given the small amount of glucocorticoid present in fludrocortisone.

**DOCP versus fludrocortisone: which is better?**

Advantages and disadvantages exist for both methods of therapy. Fludrocortisone can, in some dogs, be used without additional prednisolone, which could be an advantage for some owners. Some may prefer DOCP is given as a subcutaneous injection, whereas others may find it easier to remember to give tablets daily.

DOCP and prednisolone therapy together mean the glucocorticoid requirement and mineralocorticoid activity can be individually titrated, which should result in more effective control without side effects. This is in contrast to fludrocortisone, which can, in some dogs, result in signs of iatrogenic hyperadrenocorticism. This is because some may require very high doses to normalise their electrolytes and, ideally, Na+K ratio with the resultant overdose of glucocorticoid replacement.

After initial stabilisation, fludrocortisone can be administered when the patient is eating, whereas DOCP can be given once the patient has been rehydrated. This often means DOCP can be administered sooner. In human medicine, the standard method of monitoring hypoadrenocorticism includes serum electrolyte concentrations, blood pressure and plasma renin activity. In dogs, plasma renin activity at diagnosis is increased – compared to a control population.

In dogs treated with DOCP, the plasma renin activity decreased and normalised. In dogs treated with fludrocortisone plasma, renin activity did not change and was persistently increased.
addition, DOCP resulted in significantly higher sodium and lower potassium than those treated with fludrocortisone. These findings suggest DOCP is the preferred treatment of the two.

Most studies assessing the survival and clinical control of dogs treated with DOCP versus fludrocortisone tend to favour DOCP, but some report no statistical difference.

Summary

Exciting developments have been made in the therapy of hypoadrenocorticism, particularly after the launch of DOCP.

With further experience, it is likely better treatment and monitoring protocols will be established, resulting in better control and, ultimately, improved quality of life for dogs with hypoadrenocorticism.

- Some of the drugs mentioned are not licensed in the UK for veterinary use.

References