IMPROVING SUCCESS RATES WHEN TREATING DIABETIC KETOACIDOSIS

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Stijn Niessen discusses a systematic and informed approach for dealing with this condition in cats and dogs

Summary

This article is aimed at re-familiarising the reader with the mechanisms behind diabetic ketoacidosis (DKA) and the main principles of the successful treatment of this emergency case scenario. Special emphasis will be placed on the key steps that make the difference between life and death, satisfied and disgruntled owners and, very importantly, clinicians experiencing restless nights or leaving the practice with confidence in a good outcome.

Key words

DKA, diabetes mellitus, insulin, emergency, endocrinology

BEFORE insulin was discovered and extracted from animal pancreata, diabetic ketoacidosis (DKA) proved invariably fatal for anyone suffering from diabetes mellitus.

Even today, some reports suggest that 10 to 15 per cent of humans will die from an episode of DKA, indicating that even with gold-standard care and relatively (compared to companion animals) early detection, there will be a proportion of animals that we will not be able to save with current treatment methods.

When glucose deficiency occurs due to decreased insulinmediated uptake, the liver will start oxidation of non-esterified fatty acids as an alternative energy source.

Oxidation of free fatty acids (FFA) gives rise to acetoacetate, beta-hydroxybutyrate (B-OHbutyrate) and acetone, the ketone bodies. Conditions for increased ketogenesis include mobilisation of FFA from triglycerides in adipose tissues (which is more present in obese animals), fat synthesis in the liver and fat oxidation.

We are all familiar with (and use) the hypoglycaemic effect of insulin, but a far stronger action of insulin is its function as an inhibitor of lipolysis and FFA oxidation. Therefore, absolute or relative absence of insulin will cause lipolysis and FFA oxidation to take place uninhibited, resulting in ketogenesis.

• **Take-home message.** One of insulin's most important and strongest effects is inhibition and reversal of lipolysis and FFA oxidation, thus preventing ketogenesis.

DKA diagnosis

DKA diagnosis usually coincides with a previous or contemporary diagnosis of diabetes mellitus (DM). We also tend to see concurrent ketonuria/ketonaemia. When we use nitroprusside urine keto-sticks, we need to be aware that they measure acetoacetate and acetone – they do not measure B-OH-butyrate.

The clinical implication of this is the potential for missing our diagnosis, especially in a case of an animal with circulatory collapse. This will lead to increased lactic acid formation, a change in redox potential and, as a consequence, an increase in B-OH-butyrate and a decrease in acetoacetate. Initially, it will also produce discouraging results once treatment has been started as the B-OH-butyrate will be converted into acetoacetate, causing an increase in detection of ketone bodies using this dipstick method. The diagnosis of diabetic ketosis or diabetic ketoacidosis depends on the blood pH.

How to approach a DKA patient

When faced with a DKA patient, we first need to ask ourselves: why? Why did this happen now and not earlier? DKA patients have often been diabetic and at risk of suffering from DKA for a long time, and thus in many cases there is a particular reason why it occurred at a particular time.

Factors that may be at the root of DKA episodes happening include:

• diabetes mellitus was simply ignored due to the lack of owner-pet interaction, resulting in late or absence of noticing clinical signs associated with diabetes mellitus;

• a bout of pancreatitis;

• administration of steroids

• insulin that has been stored inappropriately, resulting in the long-term injection of inactive insulin; and

• the occurrence of concurrent (with DM) disease.

The reason why we should ask this question first is that this underlying cause might completely change our, or the owner's, approach to this emergency case.

For instance, if we are dealing with severe pancreatitis we need, apart from attending to the DKA, to think also about painrelief, plasma administration, discussing the risk of recurrence with the owner and so on.

If we are dealing with underlying disease, such as lymphoma, this obviously changes matters completely and will require thorough discussion with the owner.

Therefore, apart from treating the DKA itself, we also want to hunt for and, if found, treat any underlying disease or management issue.

• **Take-home message.** When diagnosing DKA, ask yourself: why did this happen now?

As part of the DKA treatment protocol, predisposing factors should be dealt with whenever possible.

The second question to ask is: is this animal ketotic or ketoacidotic? Hypovolaemia due to osmotic diuresis and ketogenesis can lead to a lowering of blood pH. However, many patients are in fact DK instead of DKA and are, therefore, feeling much better, often retaining their appetite.

In this scenario, we do not usually need an aggressive approach with prolonged hospitalisation, fluid therapy and hourly IM soluble insulin injections or IV insulin infusions.

If animals remain clinically healthy (and, therefore, are appetent) we can often resolve the ketotic state by adapting the normal SC insulin injection protocol (or initiating it if diabetes mellitus was not diagnosed previously). We must still resolve any underlying issues, such as lack of owner compliance, use of inactive insulin preparations, switching to bid insulin if sid, resolving infections – especially in the urinary tract – and so on.

• **Take-home message.** We need to adapt a different approach to the clinically healthy, appetent, non-acidotic yet ketotic patient when compared to the ill, inappetent, ketotic and acidotic patient.

Treatment modalities

The main treatment modalities include the following:

• IV fluid therapy *****

• insulin therapy ****

• ancillary therapy ***

• bicarbonate therapy (-)

• monitoring *****

The stars (*) indicate the relative importance of these modalities in achieving a successful outcome; (-) is a modality not routinely indicated and potentially dangerous.

Fluid therapy

Although often seen as an ancillary treatment, IV fluid therapy is deemed at least as important as insulin in a DKA patient. In certain circumstances, one could do worse than putting an overnight-arriving DKA patient on fluids first and starting insulin treatment in the morning. In fact, this is sometimes even indicated (hypokalaemic cases). Due to diabetes mellitus-induced osmotic diuresis, vomiting and inappetence, DKA patients are often volume depleted and in desperate need of treatment.

Fluid therapy will also promote the excretion of ketones, can even correct acidosis on its own and can lower blood glucose (BG). Initially at least, 0.9 per cent saline is a fair choice of fluids. The rate can range from 60ml/kg/24 hours to 100ml/ kg/24 hours, but depends on the assessment of hydration status, cardiovascular status, urine output and continued fluid loss through vomiting and/or diarrhoea.

Appropriate potassium supplementation is essential, especially once insulin treatment has been initiated (since this will further lower potassium through movement of potassium into the cells) and should be based on initial and continued measurement of potassium. If potassium measurement is unavailable or unknown, one could consider adding 40mEq (milli-equivalent) of potassium chloride (KCl/L), although this is suboptimal and referral to another location with more appropriate monitoring means should be considered.

Phosphate (PO_4) supplementation should also be considered: add if PO4 is less than 0.5mmol/L or if signs of haemolytic anaemia appear. IV infusions can consist of 0.01mmol/kg/hour to 0.03mmol/kg/hour, but have to be given in calcium-free fluids (0.9 per cent saline) to avoid

crystallisation of calcium phosphate ($CaPO_4$).

IV fluid management also includes the addition of dextrose once BG has dropped in response to our insulin treatment protocol. It should not be given until BG is less than 15mmol/L and it can be given as a five per cent dextrose/glucose infusion.

Insulin therapy for DKA patients

There is no clearly superior protocol for insulin therapy. A general rule is to pick an insulin protocol that suits your practice. However, it is worthwhile to consider whether a different protocol might suit your particular practice circumstances better. The overall success of the protocol depends on a few key factors:

• appropriate and continued monitoring;

• inducing gradual changes; and

• reducing rates or delay if you are starting with a hypokalaemic patient.

Both IM and IV protocols are suitable and both have advantages and disadvantages. SC protocols have the inherent risk of resulting in malabsorption due to the state of dehydration many DKA patients are in.

The type of insulin in ill DKA patients should be regular, neutral or soluble. Protocols with insulin glargine have been and are being investigated for feline DKA patients, but insufficient evidence is available to recommend this. Furthermore, the long-acting insulin glargine seems, intuitively, a strange choice in a situation where we need to be able to adapt insulin requirements to the patient's clinical situation on an (at least) hourly basis.

Problems have arisen with the UK supply of the Insuvet range of insulins, which could lead to shortage of Insuvet Neutral Insulin. However, alternatives are available for use in DKA cases.

Various IM protocols exist. A common successful protocol includes an initial dose of 0.2IU/ kg IM, followed by 0.1 IU/kg IM every 15 minutes for one hour, continued until BG is 10mmol/L to 15mmol/L, and then IM 0.1 IU/kg to 0.4IU/kg every 15 minutes over six to eight hours.

At this stage, if hydration status is good, SC treatment can be considered. When BG is down to this level, IV dextrose and glucose should be started at approximately one to two times maintenance.

The protocol is adapted on the basis of BG measurements of every 15 minutes one (beginning) to three hours (such as if BG is more than 15mmol/L, insulin can be increased; if BG is less than 10mmol/L, decrease insulin). Once the patient is stable, eating and happy, we can switch to

traditional insulin regimens and types.

However, one might want to consider an IV insulin protocol instead. Advantages include:

• more control over serum insulin levels;

• more predictable bioavailability;

• corrections made quickly if BG drops too quickly (this is important – see the complications section later); and

• possibly less labour-intensive and intrusive for the patient.

The initial rate of soluble insulin is 0.05IU/kg/hour to 0.1IU/ kg/hour. The way to prepare the insulin solution is the following: 25IU in a 500ml NaCl bag gives 50/1000=0.05IU/ml -> 1ml/ kg/hour and, therefore, corresponds to 0.05IU/kg/hour.

When preparing the insulin infusion, run it through a separate infusion line for approximately 30 seconds before attaching it to the patient. The aim with any protocol is a 2mmol/L BG drop per hour, not more. When BG is 10mmol/L to 15mmol/L we should halve the insulin infusion rate and start five per cent dextrose/ glucose to maintain a stable BG within this range. This allows us to continue to provide insulin since the insulin is primarily used to reverse the ketogenesis, not to lower the BG.

Once ketogenesis is reversed, the patient will feel better and start eating and we can then consider switching to SC regular insulin, 0.1 IU/kg to 0.4IU/ kg every 15 minutes over six to eight hours, since hydration status should be normalised by now. Following this, a traditional insulin protocol will be possible again.

Ancillary therapy

This is a very important part of the treatment protocol, where we attend to concurrent disease. Pancreatitis is a very important and frequent concurrent disease, and should be attended to.

The patient is not going to clinically improve if we neglect the discomfort that comes with this disease. IV fluid therapy will help here, but additionally, plasma administration, pain relief (0.01mg/kg buprenorphine SC/ IV), dietary precautions and antiemetics and/or anti-nausea drugs should be considered. Urinary tract infections and other infections should also be dealt with appropriately.

Part of this ancillary therapy is, therefore, made up of diagnostics appropriate for individual DKA patients and may include abdominal ultrasonography and feline pancreatic lipase immunoreactivity

(fPLI) or pancreatic lipase immunoreactivity (cPLI) determination.

A cystocentesis to obtain a sterile urine sample for full urinalysis, sediment examination and – regardless of sediment – culture, is also recommended. Entire diabetic animals should have neutering planned.

Bicarbonate treatment

In most cases, bicarbonate treatment is probably the least necessary part of the treatment.

In fact, it can even result in deterioration of the patient when applied where it was not indicated. In most DKA patients, correct treatment using the other treatment modalities will make bicarbonate treatment unnecessary. Both fluid therapy and insulin therapy will help resolve the acidosis. In fact, 1mEq of HCO_3- is already generated from each mEq of ketoacid that is transformed through treatment with insulin.

Adverse effects of HCO_3- treatment include worsening of hypokalaemia, paradoxical cerebral acidosis and delaying the decrease in blood lactate and ketone body levels.

If we do want to consider bicarbonate treatment, then we only do so when plasma HCO_3- is less than 12mEq/L or venous CO_2 is less than 12mmol/L.

If these values are unknown, the best rule is to not give it, unless the animal is severely ill – and then we give only one dose and focus on other treatment modalities. If values are known, one can use the following calculations: amount of HCO_3-(mEq) to give equals bodyweight (kg) × 0.4 × (12-patient HCO_3-) × 0.5.

We add this to the IV fluids and administer over six hours but definitely not as a bolus. Administration is repeated only if HCO_3-

Monitoring

The ill DKA patient represents a metabolic emergency and, therefore, will have the best chance of surviving when intensive care can be applied. This is especially so once treatment has been initiated, as the next stage is to induce many metabolic alterations that can, in themselves, cause deterioration and death if they are not induced slowly and monitored adequately.

Referral to a better-equipped or monitored facility should, therefore, be considered. A basic initial work-up can form a good basis from which a plan of action can be formulated and can guide the monitoring process. It ideally includes urinalysis, haematocrit, threshold profile, BG, venous CO_2 or arterial acid-base, BUN/ creatinine, sodium, potassium, calcium and PO_4.

Whether additional data is necessary depends on the individual patient's history, physical examination and possible concurrent disorders. This could include a more complete haematology, biochemistry, radiographs, abdominal ultrasound, fPLI or cPLI. Parameters that need to be assessed regularly include the following protocols.

• Blood glucose. Initially, it is best to monitor BG quarterly over one to two hours. Adjust insulin dosages and begin glucose/dextrose administration when BG goes below 15mmol/L.

• Hydration, respiration and pulse quarterly over two to four hours.

• Electrolytes ($K+PO_4$) with or without CO_2/acid/base every 15 minutes over four to 12 hours.

• Urine output, glycosuria and ketonuria every 15 minutes over two to four hours.

• Bodyweight (fluid overload), PCV (haemolysis), temperature (sepsis, shock and infection), systolic blood pressure (one to two per day).

• Additional monitoring according to any concurrent disease that is present.

Monitoring is quite rightly often seen as the basis of success in treating DKA patients.

• **Take-home message.**

Although insulin therapy is an obvious part of DKA treatment, fluid therapy and adequate monitoring are at least as impor tant and essential to survival of the patient.

Outcome and complications

The mortality rate of dogs and cats with DKA is described as 30 to 40 per cent.

However, these high mortality rates are usually associated with the presence of underlying disease, too aggressive treatment and/or inadequate monitoring. This emphasises the usefulness of checking for underlying disease at the start. This can avoid disappointment for clinicians, owners and pets – especially if we are dealing with underlying disease that carries a poor short-term prognosis or is likely to recur in view of its incurable nature. Indeed, recurrence can be a complication if we do not take away any underlying disease or predisposing factor.

An important complication is cerebral oedema due to rapid decreases in BG values. We can prevent this by not decreasing BG levels by more than 2mmol/L/ hour to 3mmol/L/hour and also to not decrease serum osmolality by more than 0.5osmol/hour to 1osmol/hour (osmolality=2× (Na+K)+BUN+BG).

Following the above guidelines should lead to feeling more confidence in about treating DKA patients, increasing patient survival rates and, importantly, decreasing a clinician's stress levels. The clinicians at the internal medicine service at the Queen Mother Hospital are more than happy to discuss your DKA (and other) cases with you, should you have further questions. Additionally, we are still offering free fructosamine and lipid measurements in newly diagnosed diabetic cats and fructosamine and HbA1c in diabetic dogs as part of our research.

For more information, please check out our websites: www.rvc.ac.uk/cic and www.rvc.ac.uk/QMH

A five-minute diabetes treatment survey is also still ongoing for clinicians dealing with diabetic pets and owners of insulin-treated pets (visit www.rvc.ac.uk/diabetesvet for more details).

Finally, more information on DKA and other endocrine diseases will be discussed during the "Endocrine Highlights Event", which will take place at the RVC from May 4 to 6, which might be of interest to the reader.