CASE REPORT: USE OF INSULIN GLARGINE IN THE TREATMENT OF DIABETIC KETOADIDOSIS

Relato de caso: uso de insulina glargina no tratamento da cetoacidose diabética

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Abstract

Diabetic ketoacidosis (DKA), the main complication of *diabetes mellitus*, combines hyperglycemia, metabolic acidosis, and ketosis with ketonuria, promoting clinical signs such as anorexia, weakness, pain, and tachypnea due to an increased concentration of circulating ketone bodies. The prognosis is guarded, and diagnosis is based on the association between blood measurement of β-hydroxybutyrate and blood gas analysis. Treatment involves a combination of fluid therapy and insulin therapy, aiming to decrease blood glucose and ketone body levels, correct intravascular volume and restore hydroelectrolytic/acid-base balance. Thus, the present study aims to report the case of a diabetic dog, treated for ketoacidosis, which was monitored and managed through the use of insulin glargine.

Keywords: Ketoacidosis; diabetes; insulin.

Resumo

A cetoacidose diabética (CAD), principal complicação da *diabetes mellitus*, combina hiperglicemia, acidose metabólica e cetose com cetonúria, promovendo sinais como anorexia, fraqueza, dor e taquipneia, devido ao aumento na concentração de corpos cetônicos circulantes. Desse modo, o prognóstico é reservado e o diagnóstico é realizado associando-se à mensuração sanguínea de β-hidroxibutirato e hemogasometria. O tratamento é realizado através de fluidoterapia e insulinoterapia, visando diminuir a glicemia e a concentração de corpos cetônicos, além de restabelecer o equilíbrio hidroeletrolítico/ácido-base. Assim, o presente trabalho tem como objetivo relatar um caso de um canino diabético, atendido em quadro de cetoacidose, que teve a sua conduta terapêutica baseada no uso de insulina glargina.

Palavras-chave: Cetoacidose; diabetes; insulina.

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Introduction

Diabetic ketoacidosis is a medical emergency that develops in approximately 15% of diabetic animals and is characterized by persistent hyperglycemia, metabolic acidosis, and ketosis with ketonuria (Alonso *et al*., 2022; Crivelenti *et al*., 2010; Jericó; Andrade Neto; Kogika, 2015; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019). In these cases, reduced glucose uptake by cells triggers lipolysis and mobilization of free fatty acids, leading to the production of acetoacetic acid (AcAc), which may be reduced to β-hydroxybutyrate (βHB), also acidic in nature, or decarboxylated to acetone (Alonso *et al*.,2022; Crivelenti *et al*., 2010; O'Brian, 2010; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019).

The initial clinical signs are primarily associated with diabetes mellitus, including polyuria, polyphagia, polydipsia, and weight loss, and may progress to anorexia, vomiting, diarrhea, dehydration, tachypnea, and a ketotic breath odor (Salvador, 2011; Nelson, 2015; O'Brian, 2010; Wolfran; Oyafuso; Osaki, 2019). In more severe cases, neurological alterations and even shock may occur, secondary to hypovolemia, which is triggered by fluid loss due to osmotic diuresis resulting from glycosuria, in association with vomiting and diarrhea, as well as reduced water intake and compensatory hyperventilation in response to acidosis (Alonso *et al*., 2022; Crivelenti *et al*., 2010; Nelson, 2015; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019).

Regarding diagnosis, the most appropriate tests include measurement of blood βHB (values greater than 3 mmol/L) and blood gas analysis to confirm ketoacidosis, characterized by hyperketonemia and metabolic acidosis, with blood pH lower than 7.3 and bicarbonate concentration below 15 mmol/L (Alonso *et al*., 2022; Crivelenti *et al*., 2010; Jericó; Andrade Neto; Kogika, 2015; O'Brian, 2010; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019). In addition, patients typically present with hyperglycemia, averaging 500 mg/dL, and decreased serum electrolytes due to urinary losses and emesis (Alonso *et al*., 2022; Crivelenti *et al*., 2010; Gomes *et al*., 2024; Nelson & O'Brian, 2010; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019).

Treatment of diabetic ketoacidosis aims to restore hydration, reduce blood glucose levels, reestablish fluid, electrolyte, and acid–base balance, and address precipitating factors or secondary infections (Alonso *et al*., 2022; Crivelenti *et al*., 2010; Nelson, 2015; Gomes *et al*., 2024; O'Brian, 2010; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019). One of the main pillars is fluid therapy, which corrects fluid and electrolyte imbalances and reduces the secretion of hyperglycemic hormones. The second pillar is insulin therapy, aimed at interrupting ketogenesis, promoting the metabolism of ketone bodies, reducing gluconeogenesis, and stimulating the utilization of circulating glucose (Alonso *et al*., 2022; O'Brian, 2010; Nelson, 2015; Jericó; Andrade Neto; Kogika, 2015; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019).

There is general consensus that regular insulin is the primary choice for the treatment of diabetic ketoacidosis due to its rapid onset and short duration of action, allowing for greater flexibility in dose and frequency adjustments (Alonso *et al*., 2022; Crivelenti *et al*., 2010; Gomes et al., 2024; Nelson, 2015; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019). However, a study by Marshall *et al*. (2013) concluded that insulin glargine, when administered intramuscularly, may serve as an alternative for the treatment of diabetic ketoacidosis in cats. This insulin is defined as a recombinant form of human insulin, soluble at pH 4—where it is produced and stored—but which forms precipitates upon administration, resulting in a rapid onset combined with a prolonged duration of action (Behrend *et al*., 2018).

Furthermore, studies demonstrate that both regular insulin and glargine produce nearly identical effects on the reduction of blood glucose concentrations in humans when administered intravenously, with a similar pharmacokinetic profile when administered intramuscularly (Behrend *et al*., 2018; Marshall *et al*., 2013). Finally, it is important to emphasize that insulin administration must be maintained until normalization of blood βHB levels, and blood glucose should be kept between 100 and 250 mg/dL. Concomitant administration of dextrose-containing fluids may be required to prevent hypoglycemia (Jericó; Andrade Neto; Kogika, 2015; O'Brian, 2010; Nelson, 2015).

Case Report

On December 19, 2024, a 7-year-old male neutered canine of the German Spitz breed, with a body condition score of 5/9, was presented to a veterinary clinic. During anamnesis, the owner reported that the patient had been seen at another veterinary clinic three days earlier due to vomiting, diarrhea, polyuria, and weight loss. At that time, gastroenteritis was suspected, and blood tests and abdominal ultrasonography were requested. The results revealed increased total protein (8.3 g/dL) and platelet count (714,000), bladder crystals, hepatomegaly, increased hepatic echogenicity, biliary sludge, and benign nodular hyperplasia of the liver, while the adrenal glands were of normal size. The patient was discharged with a prescription for omeprazole, meloxicam, and a symbiotic. However, clinical signs persisted, and the animal returned the following day, when hospitalization was recommended for symptomatic management.

At that time, blood glucose measurement revealed hyperglycemia (450 mg/dL), raising suspicion of diabetes mellitus. The treatment protocol included fluid therapy with lactated Ringer's solution (LRS), amoxicillin-clavulanate, dexamethasone, maropitant citrate, dipyrone, and NPH insulin at 0.5 IU subcutaneously every 12 hours. The patient remained hospitalized until December 18, when it was discharged; however, blood glucose levels remained above 393 mg/dL throughout hospitalization, including at discharge. The discharge prescription included amoxicillin-clavulanate, saline solution, puppy food, and 5 IU of NPH insulin to be administered at 08:00 a.m. and 04:00 p.m. Subsequently, the owner sought a second opinion from a veterinarian acquaintance, who recommended rehospitalization at another facility and blood gas analysis. This examination revealed metabolic acidosis (pH 7.15), low bicarbonate (11.4 mmol/L), hypokalemia (3.3 mmol/L), and hyperglycemia (222 mg/dL). The patient was then reassessed at the new clinic, presenting as depressed but alert, normocolored, with 8% dehydration, no abdominal pain, but abdominal distension, thin skin, normothermia, tachypnea, blood glucose of 260 mg/dL, and βHB of 6.4 mmol/L.

Hospitalization was initiated for management of diabetic ketoacidosis. However, due to the unavailability of regular insulin in the market, a protocol based on insulin glargine was implemented: 2 IU administered intramuscularly whenever blood glucose exceeded 150 mg/dL. This approach was based on a protocol described in feline patients, with an initial two-hour period of fluid therapy using LRS prior to insulin administration.

At admission, the patient was highly agitated, with increased blood pressure, temperature, and respiratory rate. During hospitalization, blood glucose levels gradually decreased, and vital parameters normalized. By the following day, the patient regained appetite but remained hospitalized until December 22, when βHB levels normalized (0.2 mmol/L) and blood glucose reached 140 mg/dL. At discharge, the patient was referred for specialized endocrinology follow-up for management of diabetes mellitus and investigation of hypercortisolism.

Discussion

According to Crivelenti *et al*. (2010), Salvador (2011), and Wolfran, Oyafuso, and Osaki (2019), the prevalence of diabetic ketoacidosis is associated with insulin-dependent dogs aged 5 to 12 years, particularly those with a recent diagnosis of diabetes mellitus or poorly controlled disease. This profile is consistent with the present case, in which the patient was 7 years old and had been diagnosed only a few days earlier.

Regarding concurrent diseases, pancreatitis is most commonly reported (O'Brian, 2010; Wolfran; Oyafuso; Osaki, 2019), although it was not diagnosed in this case. However, there was suspicion of hypercortisolism, another condition that may be associated.

In terms of clinical presentation, the patient exhibited polyuria, polydipsia, weight loss, anorexia, abdominal distension, dehydration, tachypnea, and vomiting, consistent with descriptions by Salvador (2011), Nelson (2015), O'Brian (2010), and Wolfran, Oyafuso, and Osaki (2019).

For diagnosis, the gold standard approach was employed, combining measurement of blood βHB with blood gas analysis, as recommended by Alonso *et al*. (2022), Crivelenti *et al*. (2010), Jericó, Andrade Neto, and Kogika (2015), O'Brian (2010), Salvador (2011), and Wolfran, Oyafuso, and Osaki (2019). Findings included βHB > 3 mmol/L, blood pH < 7.3, and bicarbonate concentration < 15 mmol/L, consistent with the literature.

Regarding treatment, fluid therapy with LRS was administered to avoid worsening metabolic acidosis, in accordance with Alonso *et al*. (2022) and Wolfran, Oyafuso, and Osaki (2019). The patient received fluids for two hours at a calculated rehydration rate prior to initiation of insulin therapy.

The main divergence from the literature relates to insulin therapy. Current consensus recommends the use of regular insulin due to its rapid onset and short duration of action (Alonso *et al*., 2022; Crivelenti *et al*., 2010; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019). However, in this case, insulin glargine—a long-acting insulin with slower onset—was used due to the unavailability of regular insulin, following the protocol described by Marshall *et al*. (2013). Despite this deviation, a superior clinical response was observed compared to the first hospitalization, during which NPH insulin had been used. The patient recovered and achieved normalization of βHB levels through administration of 2 IU of insulin intramuscularly whenever blood glucose exceeded 150 mg/dL. Although there are no specific studies detailing the absorption time of glargine via the intramuscular route, it is generally recognized that intramuscular administration leads to faster absorption compared to subcutaneous administration (Oliveira; Veloso; Camargo, 2019; Freitas *et al*., 2016). This alternative route may therefore have contributed to improved glycemic control compared to subcutaneous insulin administration.

In this case, administration of dextrose-containing fluids was not required to maintain glycemia, as described by Jericó, Andrade Neto, and Kogika (2015), O'Brian (2010), and Nelson (2015). Regarding electrolyte management, potassium supplementation was performed due to decreased circulating levels following initiation of insulin therapy, in line with Alonso *et al*. (2022), Crivelenti *et al*. (2010), Salvador (2011), and Wolfran, Oyafuso, and Osaki (2019). No additional electrolyte replacement was necessary, as other imbalances are typically corrected through fluid therapy, and bicarbonate replacement is generally contraindicated (Alonso *et al*., 2022; Jericó; Andrade Neto; Kogika, 2015; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019).

However, repeat blood gas analysis to reassess electrolyte status after treatment was not performed due to financial constraints. Although some authors recommend the use of feeding tubes (Alonso *et al*., 2022; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019), this was not necessary in the present case, as the patient resumed voluntary food intake on the second day of hospitalization.

The average hospitalization period reported in the literature ranges from 7 to 10 days (Alonso *et al*., 2022; Crivelenti *et al*., 2010; Jericó; Andrade Neto; Kogika, 2015; Nelson, 2015; Salvador, 2011; Wolfran; Oyafuso; Osaki, 2019). In contrast, clinical resolution in this case was achieved within four days of hospitalization.

Finally, the limitations of this study should be acknowledged, including the financial constraints of the patient's owner and the absence of post-discharge follow-up, either clinically or via communication, which prevented further updates on the patient's condition.

Final considerations

Based on the data obtained, insulin glargine demonstrated satisfactory results in reversing a case of diabetic ketoacidosis through the use of a protocol involving the intramuscular administration of 2 IU whenever the patient's blood glucose exceeded 150 mg/dL. This approach enabled the use of an alternative to the standard protocol, which relies on regular insulin—unavailable at the time—while achieving equally positive outcomes, with the patient progressing to discharge.

These findings highlight the need for further studies on the pharmacokinetics and pharmacodynamics of different types of insulin when administered via various routes, as well as

the development of new protocols for glycemic control and reversal of diabetic ketoacidosis. Such efforts are essential to address limitations related to drug availability in the market and financial constraints. &

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- **Conflicts of interest**: The author declares that she has no conflicts of interest.
- **Ethical approval**: The study was conducted in accordance with the ethical principles applicable to research. As this is a clinical case report involving diagnostic and therapeutic procedures performed as part of routine clinical practice, submission to the Ethics Committee was not required. The animal's legal guardian was duly informed and consented to the procedures.
- **Data and materials availability**: he data and materials used in this study are available upon request.
- **Author contributions**: Literature review and management of the reported clinical case.

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