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Comparison of continuous and intermittent glucose monitoring systems in a dog with diabetic ketoacidosis: a case report

W. Kim[1], H. Kim[1], S. Kang[1], J. Bae[1], J. Choi[1], J. Park[2], D. Yu[1]*

[1]College of Veterinary Medicine, Chonnam National University, Gwangju, Republic of Korea
[2]College of Veterinary Medicine, Chonbuk National University, Iksan, Republic of Korea

*Corresponding author: dyu@jnu.ac.kr

ABSTRACT: A Miniature schnauzer (12 years old, neutered male) was referred for lethargy, anorexia, and oral bleeding. On initial evaluation, severe hyperglycaemia (blood glucose concentration of 34.9 mmol/l), ketonuria, systemic inflammation (fever, panting, left-shift neutrophilia, and a high C-reactive protein level of 980.97 nmol/l, abnormal pancreatic lipase immunoreactivity, and periodontitis were found. With consideration of possible insulin resistance, blood glucose (BG) levels were monitored using a portable glucose meter (*q* 1–3 h) and a continuous glucose monitoring system (CGMS) for 72 h (three consecutive trials); intensive insulin therapy was initiated using regular insulin (2.2 IU/kg intravenously). The insulin doses needed, based on the nadir, peak, and duration of insulin action from a traditional intermittent glucose curve were higher than those based on the CGMS results. Meanwhile, transient hyperglycaemic and hypoglycaemic periods, occurring between the intermittent measurements, were easily identified with the CGMS. Therefore, insulin resistance and the Somogyi phenomenon are less likely to occur with use of the CGMS than with intermittent BG measurements. By comparing data from a CGMS to those from an intermittent portable BG measurement system, this case report emphasises the importance and usefulness of a CGMS.

Keywords: continuous glucose monitoring system; portable glucometer; diabetic ketoacidosis; hyperglycaemia; hypoglycaemia

Canine diabetes mellitus (DM) is a common endocrinopathy with a reported prevalence rate of 0.4–1.2% (Nelson and Reusch 2014). Because the general clinical signs of DM may not be overt or not persistent at the early state of DM, failure of early diagnosis usually allows progression to glucosuria, ketonuria, and ketonaemia. Eventually, diabetic ketosis (DK) and diabetic ketoacidosis (DKA) develop. Although the prevalence in veterinary medicine of DKA, a life-threatening complication, is unknown, 65% of dogs with DKA were newly diagnosed with DM (Hume et al. 2006). Insulin therapy is necessary as an emergency treatment, along with correction of acidosis, dehydration, electrolyte disturbances, and treatment of concurrent disorders. The administration of insulin requires frequent monitoring of blood glucose (BG) concentrations.

Conventionally, BG monitoring involves repeated sampling using a portable BG meter, every one or two hours for 24 h, to obtain a serial blood glucose curve. However, these intermittent BG measurements may not detect dramatic changes, such as a blood glucose peak or nadir, between two sampling times. Certainly, repeated venipuncture in hospitalised animal patients can cause pain and stress for the animal. Assessing the blood glucose

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levels in such an unfamiliar environment is also problematic.

A continuous glucose monitoring system (CGMS) is a monitoring device that evaluates glucose levels from a flexible sensor electrode every five minutes, and allows real-time recording of changes in glucose levels, continuously on a separate screen, for up to 72 h. The CGMS measures the change in interstitial glucose levels, which closely mimic blood glucose levels (Wiedmeyer and DeClue 2008; Surman and Fleeman 2013; Corradini 2016). The CGMS can detect and alert clinicians to short-term variations, such as hypoglycaemia, hyperglycaemia, and the Somogyi phenomenon, that may not be detected between two measurements of traditional glucose monitoring. The CGMS can also detect the overall pattern of glucose variation at a glance. Evaluation using the CGMS in 10 diabetic dogs revealed the Somogyi phenomenon, nocturnal hypoglycaemia, and a short period of hypoglycaemia in three of the dogs (Affenzeller et al. 2011).

The accuracy of the CGMS has been proven in stable DM patients that have a controlled glucose level of 5.55–13.88 mmol/l and do not exhibit any ketosis/ketoacidosis or complications; however, only a handful of studies have shown that it provides clinically precise estimates of BG levels in critically ill patients with DKA (DeClue et al. 2004; Hume et al. 2006; Reineke et al. 2010). This case demonstrates the use of the CGMS in a dog with uncontrolled DKA. The aim of this case report is to emphasise the importance of serial glucose monitoring and to confirm the usefulness of the CGMS, by comparing data from the CGMS to that obtained by a traditional BG curve.

Case description

A 12-year-old, 6.6 kg, neutered male Miniature schnauzer was referred to the Veterinary Medical Teaching Hospital for anorexia, lethargy, and oral bleeding. The local veterinarian suspected periodontitis and prescribed steroids (prednisolone 0.5 mg/kg *p.o. s.i.d.*). On presentation, the dog was alert and responsive, but was panting and displayed abdominal pain. He was also febrile (39.5 °C), with a heart rate of 140 beats per minute and a high systolic blood pressure (184 mm Hg). Oral examination revealed a lost right upper canine tooth, and bleeding was stopped by applying pressure to the lesion. Complete blood count, blood chemistry, blood gas and electrolytes, urinalysis, and abdominal ultrasonography were performed to evaluate status and to reveal symptoms.

In initial screening tests the results from complete blood count and blood film were mild anaemia with a stress leukogram and inflammation: 26.5% of haematocrit (reference range, 37.3–61.7%) and an elevated white blood cell count (71.06×10^9/l; reference range, $5.05–16.76 \times 10^9$/l), with neutrophilia (segment neutrophils, 25×10^9/l; reference range, $2.95–11.64 \times 10^9$/l), a left shift (band neutrophils, 7×10^9/l; reference range, $0–1 \times 10^9$/l), lymphopaenia (0.8×10^9/l; reference range, $1.05–5.1 \times 10^9$/l), monocytosis (4.5×10^9/l; reference range, $0.16–1.12 \times 10^9$/l), and mildly toxic neutrophil changes (basophilic cytoplasm, Dohle bodies) on microscopic examination. Significant changes in chemistry profiles, blood gas analysis and urinalysis are listed in Table 1: hyperglycaemia (34.9 mmol/l) with compensatory metabolic acidosis and a high anionic gap were present; high pancreatic enzyme activities and hypercholesterolaemia were strong indications of pancreatitis; increased liver enzyme activities were observed probably due to steroid administration or severe pancreatitis; urinalysis suggested renal loss of glucose, ketone, and protein. Abdominal ultrasound evaluation revealed evidence of oedema in the right and left pancreatic lobes and right upper mesenteric area, with heterogeneous echogenicity (Figure 1). The canine pancreatic lipase immunoreactivity test (SNAP cPL, IDEXX, Westbrook, USA) was abnormal, and the C-reactive protein concentration was increased (980.97 nmol/l; reference range, 0–190.48 nmol/l, canine CRP test kit, LifeAssays AB, IDEON Science Park, SE-223 70 Lund, Sweden). The canine pancreatic lipase concentration was 515 µg/l (reference range, 0–200 µg/l) and the fructosamine concentration was 530 µmol/l (reference range, 177–314 µmol/l), based on the Spec cPL and fructosamine test (IDEXX, Westbrook, USA).

Diabetic ketoacidosis, acute pancreatitis, hypercortisolaemia, and periodontitis were diagnosed based on the initial evaluation. Primary treatment for stabilisation involved pain control (butorphanol, 0.3 mg/kg *i.v.* and a fentanyl patch, 2.1 mg/patch) and fluid therapy with antibiotic drug administration (amoxicillin/clavulanic acid 12.5 mg/kg *i.v.*, enrofloxacin 5 mg/kg *i.m.*). With consideration for possible insulin resistance from the systemic inflam-

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Table 1. Initial chemistry profiles, urinalysis, and blood gas analysis on the day of presentation and after discharge

	Parameter	Result on admission	Result after discharge	Reference interval
Chemistry profile and urinalysis	ALT (μkat/l)	0.63	2.22	0.17–1.67
	ALP (μkat/l)	> 33.40	0.72	0.38–3.54
	GGT (μkat/l)	0.73	0	0–0.12
	amylase (μkat/l)	> 41.75	17.30	8.35–25.05
	lipase (μkat/l)	94.39	10.50	3.34–30.06
	glucose (mmol/l)	34.9	5.33	3.89–7.9
	cholesterol (mmol/l)	9.19	4.45	2.85–8.29
	BUN (mmol/l)	15.4	8.57	2.5–9.6
	creatinine (μmol/l)	115	70.7	44.2–159
	total bilirubin (μmol/l)	17.1	1.7	0.0–15.4
	urine glucose (mmol/l)	55.5	negative	negative
	urine ketone (mmol/l)	4.9	negative	negative
Blood gas analysis	pH	7.283	7.394	7.335–7.446
	PCO_2 (mm Hg)	25.2	28.4	32.0–49.0
	HCO^{3-} (mmol/l)	12.0	17.5	18–24
	anion gap (mmol/l)	29.0	18.75	12–24
	base excess (mmol/l)	–14.9	–7.6	–2–0

ALP = alkaline phosphatase, ALT = alanine aminotransferase, BUN = blood urea nitrogen, GGT = gamma-glutamyltransferase, PCO_2 = partial pressure of CO_2, UPC = urine protein creatinine ratio, USG = urine specific gravity

mation and steroid administration (Hess 2010), we decided to discontinue the steroid administration prescribed by the private clinic, and to closely monitor BG levels in response to insulin. Intensive insulin therapy with regular insulin, continuous rate infusion of 2.2 IU/kg, was administered intravenously to regulate BG levels for the first two days. The dog's BG levels were monitored with a portable glucose meter (Accu-chek®, Roche, Indianapolis, USA) every 1–3 h and with a CGMS (Guardian real-time CGMS, Medtronic, Northridge, USA) for 72 h. For data

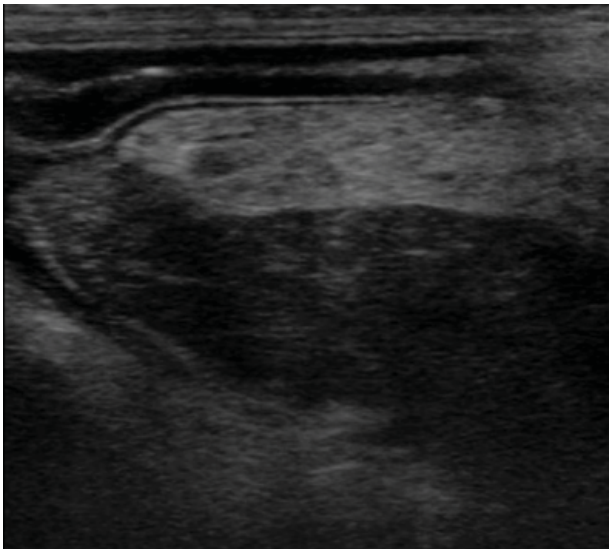

Figure 1. Abdominal ultrasound. Apparent enlargement of the right pancreatic lobes with irregular margin and decreased heterogeneous echogenicity and oedema of right upper mesenteric area

comparison, CGMS graphs from the manufacturer's software were retrieved, and then intermittent BG measurements using the portable device were superimposed retrospectively. This process could assist in determining how well the CGMS reflects the dog's glucose fluctuation in the clinical setting compared with BG measurements using the portable device (Figure 2). The portable blood glucose meter and the CGMS were calibrated with laboratory equipment that uses the glucose oxidase (gold standard) method to measure the blood glucose concentration.

According to the conventional BG monitoring, the dog's BG level was well controlled, and he was discharged with a prescription for neutral protamine Hagedorn (NPH; 0.5 IU/kg *s.c. q* 12 h). However, he was presented again, two days later, with hyperglycaemia (31.2 mmol/l (562 mg/dl)), anorexia, severe polyuria/polydipsia, abdominal pain, and lethargy (Figure 3). The insulin (NPH) dose was increased, based on the nadir, peak, and duration of glucose levels on the traditional intermittent glucose curve, starting at a dose of 0.5 IU/kg *s.c.* and increasing up to 1.0 IU/kg *s.c.* However, transient hypo- and hyperglycaemia were identified on the CGMS between the intermittent BG measurements (Figures 2A and 2B). Therefore, by comparing the BG curves from the portable glucometer and the CGMS, we determined that a different insulin regime would be followed.

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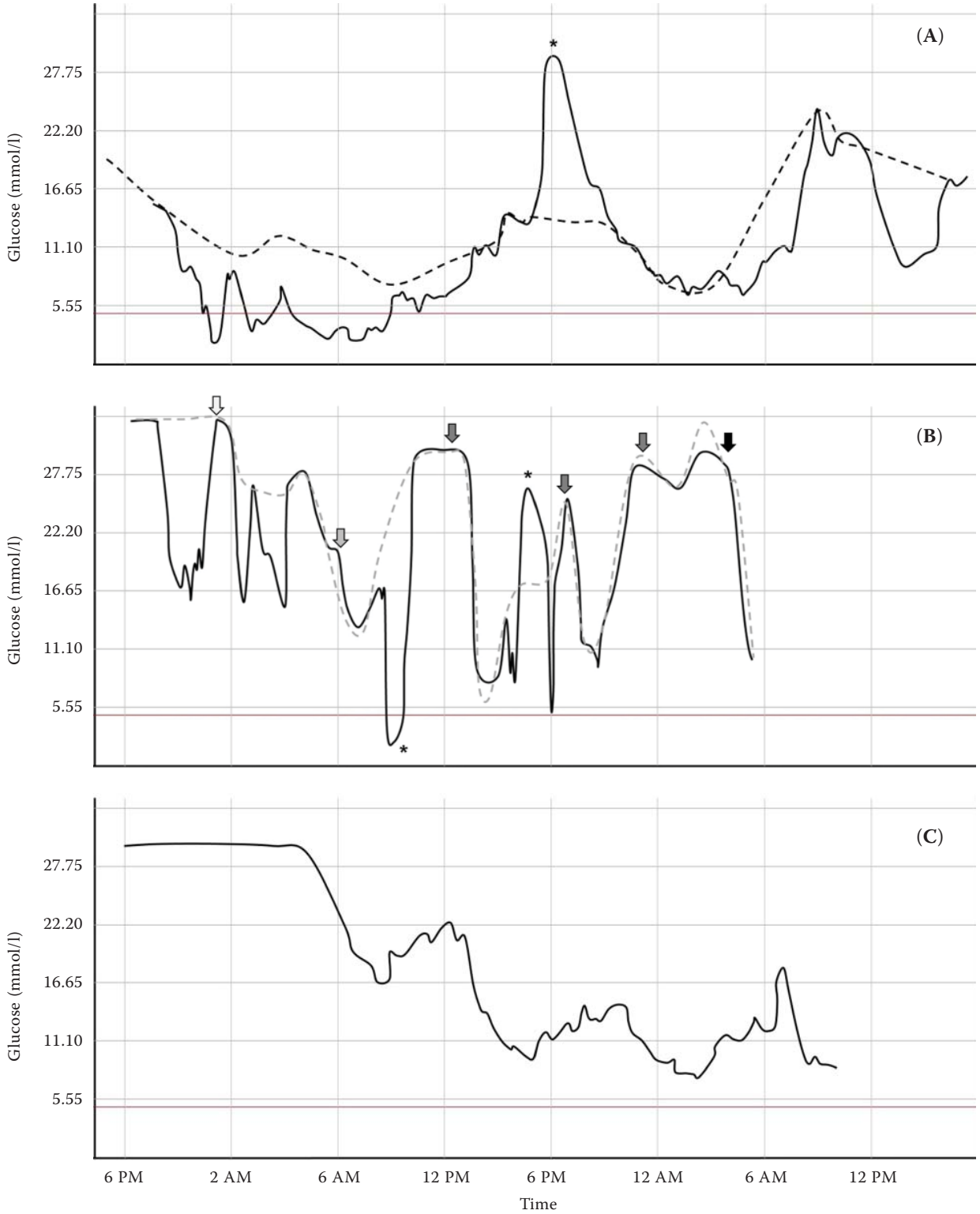

Figure 2. The 1st glucose curve (**A**) and 2nd glucose curve (**B**) drawn with the results of the portable glucose meter (dot line) and continuous glucose monitoring system (CGMS; solid line). The results of CGMS revealed hyperglycaemia and hypoglycaemia undetected by a portable device (asterisk). The 3rd glucose curve (**C**) was graphed at home after discharge. The maximum CGMS value is 22.2 mmol/l and the parts above the maximum were estimated (smooth line). The red line shows the range below 4.44 mmol/l. The arrow indicates the insulin dose administered (light grey arrow – 0.5 IU/kg, grey arrow – 0.7 IU/kg, dark grey arrow – 0.9 IU/kg, black arrow – 1.0 IU/kg)

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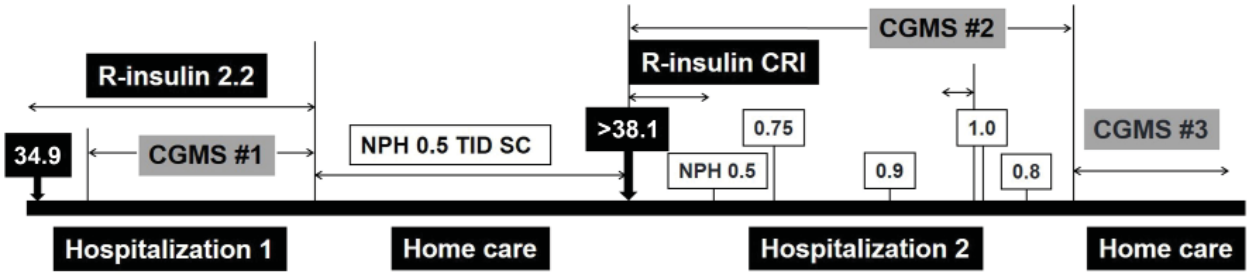

Figure 3. Time line. Blood glucose levels were monitored with a portable glucose meter (*q* 1–3 h) and with a continuous glucose monitoring system (CGMS) for three trials. Insulin dose was increased based on the result of the glucose curve with the portable device. Insulin dosage unit for regular (R-) insulin and neutral protamine Hagedorn (NPH) is IU/kg and blood glucose unit is mmol/l

We compared the intermittent BG curve, on which the initial NPH dose was determined, to the CGMS curve. The CGMS curve revealed a hypoglycaemic period between two measurements and a Somogyi phenomenon that occurred due to the intensive insulin therapy. With the appropriate insulin dose based on the CGMS, the dog was discharged for home-care with NPH (0.8 IU/kg *s.c. q* 12 h), which is a lower dose than that determined using the intermittent BG curve. The dog's condition improved after proper control of the BG levels and correction of the acid-base disturbance.

DISCUSSION AND CONCLUSIONS

In this case report, we have described how the CGMS could identify a severe hypoglycaemic period, which was previously undetected, and could be used to create an overall blood glucose graph of the effects of the insulin therapy. The interval in which the nadir was thought to be elevated in response to an insulin dose, was actually a hypoglycaemic period, while the hyperglycaemic peak was the countereffect. Without noticing this Somogyi phenomenon, the insulin therapy became more intensive. In critically ill human patients, intensive insulin therapy has been performed to maintain a euglycaemic state (4.44–6.11 mmol/l). However, research concerning the association between hypoglycaemia and death among 6026 critically ill patients receiving insulin therapy found that moderate-to-severe hypoglycaemia was strongly correlated with a high risk of death. Furthermore, particularly in hypoglycaemic patients without insulin therapy, hypoglycaemia seems to indicate an imminent death, rather than to be a cause of death (The NICE-SUGAR Study Investigators 2012). The dog in this case had several risk factors for severe hypoglycaemia that could be prevented if the BG levels were monitored in real-time with a CGMS. As such intensive insulin therapy in critically ill human patients is performed with caution, it appears wise in veterinary medicine to manage BG levels with a CGMS in unstable dogs with DKA. This allows the clinician to focus not only on the control of hyperglycaemia, but also on the prevention of a hypoglycaemic crisis.

Hypoglycaemia is a common state in critically ill dogs and cats without endogenous or iatrogenic hyperinsulinaemia, such as those with a portosystemic shunt, paraneoplastic syndrome, neonatal hypoglycaemia, xylitol toxicity, or sepsis (Miller et al. 1980; Dunayer 2004; Zini et al. 2007; Collings et al. 2012). When a hypoglycaemic event is not identified, the animal may experience seizure, critical brain damage, coma, and even death (Loose et al. 2008). Although many incidences of unrecognised hypoglycaemia occur in veterinary medicine, the cause of the neurological signs associated with hypoglycaemia is not clear. The monitoring of hypoglycaemic patients with a CGMS has been applied only in human studies. In diabetic patients, researchers revealed that patients undergoing CGMS monitoring experienced hypoglycaemia 21% less of the time, hyperglycaemia 24% less of the time, and remained at the target BG range 24% more of the time, compared to patients who received the conventional treatment (Garg et al. 2006). As this case study implies, the possible risk of unrecognised hypoglycaemia in diabetic patients in intensive care requires attention, and a prospective randomised trial of a real-time CGMS found that the relative risk for severe hypoglycaemia was 86% less in the real-time CGMS group (Joubert and Reznik 2012). The CGMS is useful not only in diabetic hypogly-

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caemia monitoring, but also in human paediatrics; it could detect 215 out of 265 episodes (81%) of infant hypoglycaemia, which were not verified with blood glucose measurements (Harris et al. 2010). Furthermore, the CGMS showed a reasonable accuracy and allowed clinicians to identify and prevent hypoglycaemia, so that BG levels were well-controlled in children with septic shock (Prabhudesai et al. 2015). This study of Prabhudesai et al. (2015) showed that real-time CGMSs may be unaffected by vasopressors, steroids, and physiological changes, such as oedema and acidosis. Furthermore, the use of real-time CGMSs is being studied in diabetic patients with hypoglycaemia unawareness, a condition of impaired counter-regulatory response, that arises due to frequent hypoglycaemic episodes (Choudhary et al. 2013). This condition significantly increases the risk of severe hypoglycaemia and mortality in patients with DM. If the comprehensive BG levels had not been monitored, the dog in this case report may have experienced repetitive hypoglycaemic episodes. This could then have resulted in hypoglycaemic unawareness, and he could have been in a dangerous situation. Hypoglycaemic unawareness is another important issue, underappreciated in veterinary medicine, that should be further evaluated.

The accuracy of CGMSs has been evaluated in dogs and cats, although there are only a few reports. Reineke et al. (2010) assessed the CGMS data from dogs and cats with DKA on the Clarke and Consensus error grids; 96.7% and 99.0%, respectively, of the CGMS data fell inside the clinically acceptable levels (Zone A and B errors). These authors determined the accuracy of the CGMS, based on the severity of ketosis, hydration, and perfusion. Only hydration had a weak association, which is unlikely to be clinically relevant. While few animal studies have been done, the reliability of CGMSs in critically ill patients is an area of active research. The results to date have revealed a strong correlation between arterial reference blood glucose and better performance, compared with point-of-care devices (Corstjens et al. 2006; Hoedemaekers et al. 2008; Holzinger et al. 2009; Brunner et al. 2011). These studies pointed out that the accuracy of CGMSs becomes diminished in the hypoglycaemic range. Because identifying hypoglycaemia is crucial to critically ill patients, the use of CGMSs in the ICU is being debated. One study concerning real-time CGMSs in 19 children with septic shock analysed the accuracy over different ranges and found it to be poor when the BG concentration was under 3.89 mmol/l (70 mg/dl) (Prabhudesai et al. 2015). The CGMS also failed to detect 76% of the hypoglycaemic states. Meanwhile, a larger scale study in 174 critically ill patients revealed a Pearson correlation coefficient of 0.92 when compared to arterial BG levels. Insulin titration error grid analysis to assess the clinical safety of the CGMS demonstrated that more than 99% of determinations were in clinically acceptable zones (Brunner et al. 2011). The purpose of using CGMSs is to predict hypo- and hyperglycaemic states, so accurate measurement at the extreme ranges is important. Point-of-care devices widely used in intensive care tend to overestimate glucose levels and, therefore, may result in a falsely high BG level determination. The hypoglycaemia in this case was overlooked on the glucose curve drawn with a portable glucose meter and seemed to be masked by overestimated values. However, the CGMS in this case detected hypoglycaemic events well enough to prevent inappropriate insulin administration. Continuous invasive blood glucose measurements have practical limitations; therefore, the accurate, easy-to-use and reliable method of glucose level monitoring provided by the CGMS would appear to be the rational choice in critical care. However, the accuracy of CGMSs in critically ill dogs and cats at extreme glycaemic ranges needs to be further researched.

In critically ill dogs and cats with DM, precise control of blood glucose concentrations with appropriate insulin therapy is crucial to improve hypoglycaemic status, and to reduce morbidity and mortality. This case report demonstrates that the CGMS can identify a severe hypoglycaemic period, previously undetected, and create a blood glucose graph demonstrating the effects of insulin therapy on the glucose levels. Even outside of critical care medicine, more accurate insulin dose adjustments could be achieved using a CGMS curve in diabetic patients. Further clinical studies using CGMSs are warranted, and many factors remain to be investigated in patients with altered BG levels.

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