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Abstract: With the aim to improve current therapeutic and monitoring options for diabetic cats, the present study compared pharmacodynamic parameters of protamine zinc insulin (PZI) and insulin degludec and validated the continuous glucose monitoring system (CGMS) iPro2 with Sof-sensor and Enlite-sensor focusing on the low glycemic range. Three doses (0.1, 0.2 and 0.3IU/kg) of the two insulin preparations and the CGMS iPro2 with two different sensors were tested in six healthy cats. After each insulin administration, onset of action, time to glucose nadir and duration of action were calculated by measuring glucose concentrations with a portable blood glucose meter (PBGM). After sensor placement, paired PBGM and sensor glucose measurements were done and analytical and clinical accuracy were calculated according to the ISO 15197:2013 criteria. Onset of action, time to glucose nadir and glucose nadir were similar for both insulin formulations. Duration of action of insulin degludec was significantly longer than those of PZI at 0.1IU/kg (P=0.043) and 0.2IU/kg (P=0.043). Overall, 166/191 (87%) Sof-sensor measurements and 106/121 (88%) Enlite-sensor measurements met ISO criteria for analytical accuracy, and all sensor measurements fulfilled ISO criteria for clinical accuracy. Insulin degludec was well tolerated in healthy cats and showed longer duration of action than PZI. Further studies on the use of insulin degludec in diabetic cats might be recommended. Both sensors had good clinical accuracy, when used with the CGMS iPro2, but the analytical accuracy was below the minimum set by ISO 15197:2013.

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Comparison of the pharmacodynamics of protamine zinc insulin and insulin degludec and validation of the continuous glucose monitoring system iPro2 in healthy cats

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Abstract

With the aim to improve current therapeutic and monitoring options for diabetic cats, the present study compared pharmacodynamic parameters of protamine zinc insulin (PZI) and insulin degludec and validated the continuous glucose monitoring system (CGMS) iPro2 with Sof-sensor and Enlite-sensor focusing on the low glycemic range.

Three doses (0.1, 0.2 and 0.3 IU/kg) of the two insulin preparations and the CGMS iPro2 with two different sensors were tested in six healthy cats. After each insulin administration, onset of action, time to glucose nadir and duration of action were calculated by measuring glucose concentrations with a portable blood glucose meter (PBGM). After sensor placement, paired PBGM and sensor glucose measurements were done and analytical and clinical accuracy were calculated according to the ISO 15197:2013 criteria.

Onset of action, time to glucose nadir and glucose nadir were similar for both insulin formulations. Duration of action of insulin degludec was significantly longer than those of PZI at 0.1 IU/kg ($P = 0.043$) and 0.2 IU/kg ($P = 0.043$). Overall, 166/191 (87%) Sof-sensor measurements and 106/121 (88%) Enlite-sensor measurements met ISO criteria for analytical accuracy, and all sensor measurements fulfilled ISO criteria for clinical accuracy.

Insulin degludec was well tolerated in healthy cats and showed longer duration of action than PZI. Further studies on the use of insulin degludec in diabetic cats might be recommended. Both sensors had good clinical

42 accuracy, when used with the CGMS iPro2, but the analytical accuracy was
43 below the minimum set by ISO 15197:2013.
44

Keywords

Protamine zinc insulin; insulin degludec; iPro2; Sof-sensor; Enlite-sensor; continuous glucose monitoring system

Abbreviations

CGMS	continuous glucose monitoring system
DM	diabetes mellitus
ISO	international organization for standardization
PBGM	portable blood glucose meter
PZI	protamine zinc insulin

1. Introduction

Insulin is the cornerstone of treatment of cats with diabetes mellitus (DM). Duration of insulin action was reported to be the most important factor, that influences choice of insulin (Smith et al., 2012). A protamine zinc preparation (PZI) for use in cats recently became available on the European market. It is an intermediate to long-acting recombinant human insulin that has been shown to be effective in diabetic cats (Nelson et al., 2009; Norsworthy et al., 2009; Ward et al., 2015), but information about its pharmacodynamics in cats is scarce. Insulin degludec is a new ultra-long acting human insulin analogue. The formulation with a concentration of 100 IU/mL is available on the market and could be used in diabetic cats. Compared with insulin glargine, insulin degludec has a predictable and stable glucose-lowering effect with fewer episodes of hypoglycemia in human patients with type 1 or type 2 DM (Birkeland et al., 2011; Heller et al., 2012; Rodbard et al., 2013). Moreover, when given three times a week, insulin degludec provides glycemic control comparable to once-daily treatment with insulin glargine (Zinman et al., 2011). To our knowledge, there are no reports of the glucose-lowering effects of insulin degludec in cats.

The generation of glucose curves is commonly used by veterinarians to evaluate feline diabetic control (Smith et al., 2012). It helps in the identification of hypoglycemia, and supports the decisions on treatment adjustments. However, glucose curves have some limitations, even if the glucose measurements are obtained in the cat`s home environment. They do

not provide continuous information about blood glucose concentrations, or the glucose nadir and the glucose peak could be missed. In addition, the duration of action of the insulin cannot be determined if home monitoring is limited to a short period of time (i.e., <12 h). Another important limitation is that not all owners are able to collect blood from their cats and generate blood glucose curves.

Real-time continuous glucose monitoring systems (CGMS) continuously measure the glucose concentration in the subcutaneous fat via a sensor containing glucose oxidase and immediately display recorded values on a monitor. These systems are considered useful for monitoring cats with DM (Ristic et al., 2005; Moretti et al., 2010; Dietiker-Moretti et al., 2011; Gough et. al., 2013; Hafner et al., 2013; Surman and Fleeman, 2013). However, CGMSs are not suitable for home-monitoring because the maximum distance between the cat and monitor should be only a few meters (Dietiker-Moretti et al., 2011; Hafner et al., 2013). The CGMS iPro2 was designed to measure and record glucose values in humans for up to 7 days without displaying the data on a monitor; instead, at the end of the monitoring period, the data are uploaded on a computer and evaluated retrospectively. Because the iPro2 does not involve a monitor, it may be suitable for use in diabetic cats in their home environment. Two different sensor types are available, the enhanced Enlite-sensor and the Sof-sensor; the former is shorter, more flexible and more accurate than the latter (Siegmund et al., 2011). In human patients, the Enlite-sensor tends to measure glucose levels lower than the reference over the entire glucose range, whereas the Sof-

103 sensor measurements tend to be higher than reference values in the
104 hypoglycemic range and lower than reference values in the hyperglycemic
105 range (Calhoun et al., 2013). The use of the CGMS iPro2 and its reliability
106 using these two sensors have not been described in cats.
107 The aims of the study were to compare pharmacodynamic parameters of
108 PZI and insulin degludec in cats, including onset of action, time to glucose
109 nadir, glucose nadir and duration of action. Furthermore, ease of use,
110 tolerability, side effects, reliability, and the accuracy of CGMS iPro2 using
111 the two different sensors were evaluated. Particular attention was paid to the
112 accuracy of the iPro2 in the low glycemic range, because reliability of
113 measurements is crucial in hypoglycemic cats.

2. Materials and Methods

2.1 Animals

Six healthy purpose-bred, neutered male, domestic shorthair cats were used. The median age was 3.7 years (range 3.4-3.7) and median body weight was 5.0 kg (range 4.7-5.9). All cats had body condition score of 5 on a 9-poin scale. They were housed in groups of two, and were fed a commercial dry food for adult cats twice daily. Food intake was adjusted to maintain a stable body weight. During the 24 h before and after insulin administration, the cats were individually kept in cages routinely used for hospitalized animals. Food was withheld for 10 h before and 24 h after insulin injection. Cats had free access to water. The study protocol was approved by the veterinary office of the canton Zurich (permission number: 110/2014).

2.2 Evaluation of two insulin preparations

PZI 40 IU/mL (ProZinc, Boehringer Ingelheim, Basel, Switzerland) and insulin degludec 100 IU/mL (Tresiba, Novo Nordisk Pharma, Küsnacht ZH, Switzerland) were tested in a randomized crossover trial. Each cat received 0.1, 0.2 and 0.3 IU/kg of PZI and insulin degludec SC, respectively, two weeks apart. Insulin syringes with 0.5 IU markings (Omnican 20, U-40 insulin, BBraun, Melsungen, Germany; BD MicroFine 0.3 ml, U-100 insulin, BD Medical, Le Pont de Claix, France) were used. The dose was rounded up to the nearest half unit. Capillary blood glucose was measured at the inner pinna of an ear with a portable blood glucose meter (PBGM) AlphaTRAK2 (Abbott Animal Health, Baar, Switzerland) 30 and 5 minutes

before and 30, 60, 90, 120, 180, 240, 300 and 360 minutes after insulin injection and then every 2 h for another 18 h. Biochemical hypoglycemia was defined as blood glucose <3.6 mmol/L.

If hypoglycemia caused vocalization, vomiting, tremors, or seizures, cats received canned food with glucose syrup (Jubin®, Andreas Jubin Pharma, Bochum, Germany), or 50% glucose solution (0.5-1 mL/kg) was infused intravenously. Hypoglycemia was not corrected, if only reduced physical activity was observed.

Onset of insulin action, time to glucose nadir, and duration of insulin action were calculated as described by Clark et al. (2012). The onset of insulin action was defined as the interval between insulin administration and the first glucose concentration that was at least 2 standard deviations lower than baseline. The time to glucose nadir was defined as the interval between insulin administration and the lowest measured glucose concentration. The duration of insulin action was defined as the interval between the onset and the end of insulin action, when measured glucose concentrations had returned to within 2 standard deviations of baseline. The glucose data were withdrawn from the calculation, if the insulin tests were terminated (feeding, infusion of glucose solution), or if the onset of action could not be achieved.

2.3 Technical features of the CGMS iPro2 and the two sensors

The CGMS iPro2 (Medtronic, Münchenbuchsee, Switzerland) consists of a digital recorder (Fig.1a) and a disposable sensor. The Sof-sensor

(Medtronic, Münchenbuchsee, Switzerland) is 14.7 mm long and has a volume of 3.6 mm^3 (Fig. 1b). It is inserted through the skin into the subcutaneous fat by means of a 17 mm 22 G needle at an angle of 45-60° and is fully hydrated within 10-15 minutes after positioning. The enhanced Enlite-sensor (Medtronic, Münchenbuchsee, Switzerland) is 9.6 mm long and has a volume of 0.2 mm^3 (Fig.1c). It is inserted by means of a 10.5 mm 27 G needle at a 90° angle and is fully hydrated within 5 minutes after positioning. Both sensors measure the interstitial glucose concentration in the subcutaneous fat via an electrode that contains glucose oxidase (Hafner et al., 2013). The iPro2 measures glucose concentrations between 2.2 and 22 mmol/L every 5 minutes for up to 7 days. Data analysis is done using the CareLink iPro software (Medtronic, Münchenbuchsee, Switzerland).

2.4 Evaluation of CGMS with two sensors

The cats were alternately implanted with a Sof-sensor or an Enlite-sensor 24 h before the insulin injection. The insertion and removal of the sensors were performed without sedation. Each sensor was placed in the subcutaneous tissue of the neck area on the right side and secured with cyanoacrylate adhesive (Cyanolit universal classic, 3M Consumer Healthcare, Rüschlikon, Switzerland) as described previously (Hafner et al., 2013). The recorder was connected to the sensor, initialized and then secured using a 3×7 cm piece of adhesive tape (Fig.1d). The video in the E-book chapter (Rand and Gottlieb, 2017) contains detailed information about placement of the glucose sensor and iPro2-recorder. Calibrations were achieved by measuring capillary

186 blood glucose concentrations 1 and 3 h after insertion of the sensor and then
187 every 8-12 h. Blood glucose concentrations were determined by use of the
188 PBGM AlphaTRAK2 previously evaluated for use in diabetic cats
189 (Cohenen et al., 2009; Zini et al., 2009). Each cat carried the sensor and the
190 recorder on it for seven days. Thereafter, they were gently removed from the
191 skin, and the glucose curve was downloaded. Ease of use of the sensors,
192 tolerability, reliability of the measurements and side effects were recorded.
193
194 **2.5 Statistical analysis**
195 Results are reported as median and range or as percentage, as appropriate.
196 Differences in pharmacodynamic parameters (onset of insulin action, time
197 to glucose nadir, glucose nadir and duration of insulin action) between the
198 same doses of two insulin preparations were analyzed using the Wilcoxon
199 matched pairs signet rank test. The Friedman test was used to compare three
200 different doses of one insulin formulation. Analytical and clinical accuracy
201 of the sensors was calculated conforming to the international organization
202 for standardization (ISO) 15197:2013 using Bland and Altman diagrams
203 and consensus error grid coordinates, respectively (Bland and Altman,
204 1986; Clarke et al., 1987). Accordingly, to be considered accurate, at least
205 95% of glucose readings had to fall within ± 0.83 mmol/L of those
206 measured with the reference method for concentrations <5.5 mmol/L or
207 within ± 15% for concentrations ≥5.5 mmol/L, and at least 99% of readings
208 had to be in zones A and B of the consensus error grid. To address the
209 clinical importance of hypoglycemia, glucose curves with concentrations

predominantly <3.6 mmol/L were chosen for analysis. Paired glucose readings from the PBGM and the two sensors were divided into a group with PBGM readings <5.5 mmol/L and a group with PBGM readings ≥5.5 mmol/L. Additionally, Spearman correlation coefficients (rho) were calculated for paired glucose readings. Differences were considered significant at $P<0.05$. A commercial software (GraphPad PRISM 6, GraphPad Software, La Jolla, USA) was used for analysis.

3. Results

3.1 Evaluation of PZI and insulin degludec

Protamine zinc insulin and insulin degludec were well tolerated by all cats and there were no injection site reactions. If the glucose lowering effect could be achieved, all three doses of both insulin formulations caused transient mild weakness, that was associated with biochemical hypoglycemia and resolved without treatment within 1-3 h in all cats. The onset of insulin action could not be achieved in three different cats treated with 0.1 IU/kg of PZI (one cat), 0.1 IU/kg of insulin degludec (one cat), and 0.2 IU/kg of PZI (one cat). At the highest dose (0.3 IU/kg), PZI caused hypoglycemia, and vomiting in 3/6 (50%) cats; one of these cats had the same reaction after 0.3 IU/kg of insulin degludec. The hypoglycemia was corrected by feeding in three cats, and the glucose data were withdrawn from the calculation. One cat treated with 0.3 IU/kg of PZI quickly recovered without any interventions.

Medians and ranges of pharmacodynamic parameters of both insulin formulations are shown in Table 1. Blood glucose curves are presented in Fig. 2 (a-f). Equal doses of PZI and insulin degludec did not differ with respect to glucose nadir, onset of action, and time to glucose nadir. Median duration of action was significantly shorter for 0.1 IU/kg of PZI (7 h; range 1.5-7) than for 0.1 IU/kg of insulin degludec (11 h; range 9-22.5) (P=0.043) and for 0.2 IU/kg of PZI (6.8 h; range 4.5-10.5) than for 0.2 IU/kg of insulin degludec (12.5 h; range 8.0-20.0) (P=0.043). However, there were no

240 significant differences in the duration of action between two insulin
241 formulations at 0.3 IU/kg.
242 The duration of action of PZI never reached 12 h, while that of insulin
243 degludec was ≥12 h in two cats with 0.1 IU/kg and in three cats with 0.2 and
244 0.3 IU/kg (data not shown). Glucose nadir, onset of insulin action, time to
245 glucose nadir, and duration of insulin action of PZI and insulin degludec
246 were similar between different doses of each insulin formulations.
247
248 **3.2 Evaluation of CGMS with the Sof-sensor and Enlite-sensor**
249 The use of a total of 36 sensors (18 Sof and 18 Enlite) was scheduled.
250 However, we used 48 sensors (24 Sof and 24 Enlite), because some sensors
251 had to be replaced. Twenty of twenty-four (83%) Sof-sensors and 17/24
252 (71%) Enlite-sensors were properly placed and initialized. The remaining 11
253 sensors failed because of faulty manufacturing (1 Sof and 2 Enlite) or lack
254 of initialization (3 Sof and 4 Enlite). One Enlite-sensor was bent during
255 insertion. Both sensor types were easy to place and well tolerated by all
256 cats. Abnormal behavior related to the sensors did not occur. All cats had
257 mild local erythema after sensor removal, which resolved spontaneously
258 within 12-24 h. One cat had a small dry scratch wound in the skin at the
259 caudal border of the Sof-sensor and another cat had a similar wound at the
260 caudal border of the Enlite-sensor. Both healed without treatment within 7-
261 10 days after sensor removal.
262 Glucose concentrations were recorded by all 20 properly placed and
263 initialized Sof-sensors and by 13/17 (76%) Enlite-sensors. Four (24%)

Enlite-sensors failed to record glucose concentration, because the recorder malfunctioned (two cats), the cat removed the sensor 1 h after insertion or for unknown reasons (one cat). Seventeen of the twenty (85%) functioning Sof-sensors and 6/13 (46%) functioning Enlite-sensors recorded the glucose concentration during the entire 7-day study period. The remaining 3/20 (15%) functioning Sof-sensors and 3/13 (23%) Enlite-sensors recorded glucose concentrations during at least 50% of the study period. The four (31%) other functioning Enlite-sensors recorded glucose concentration during <50% of the study period.

Uninterrupted recording of glucose concentrations occurred in 8/20 (40%) functioning Sof-sensors and in 8/13 (66%) functioning Enlite-sensors. Overall, there were 27 and 23 interruptions with the Sof-sensor and the Enlite-sensor, respectively. Twenty-three of the twenty-seven (85%) interruptions that occurred with the Sof-sensor and 16/23 (70%) that occurred with the Enlite-sensor lasted <1 h. The remaining four (15%) interruptions with the Sof-sensor and seven (30%) with the Enlite-sensor lasted between 1 and 24 h.

A total of 191 paired PBGM-Sof-sensor and 121 paired PBGM-Enlite-sensor glucose measurements were analyzed. One hundred and seventy-seven of one hundred and ninety-one (93%) Sof-sensor measurements and 113/121 (93%) Enlite-sensor measurements were between 2.2 and 5.5 mmol/L. The remaining measurements were equal to 5.5 mmol/L or in the range between 5.5 and 22 mmol/L. The differences between glucose measurements from the PBGM and the two CGMS iPro2 sensors are shown

288 in Fig. 3. Considering the paired glucose measurements <5.5 mmol/L,
289 160/177 (90%) Sof-sensor measurements and 102/113 (90%) Enlite-sensor
290 measurements were within ± 0.83 mmol/L of the reference method and met
291 the ISO accuracy criteria. Of the paired glucose readings ≥5.5 mmol/L, 6/14
292 (43%) of Sof-sensor measurements and 4/8 (50%) Enlite-sensor
293 measurements were within ± 15% of the reference method and met the ISO
294 accuracy criteria. Overall, 166/191 (87%) Sof-sensor measurements and
295 106/121 (88%) Enlite-sensor measurements met the ISO criteria for
296 analytical accuracy. All glucose concentrations measured with both sensors
297 were in zone A or B of the consensus error grid coordinates and met the ISO
298 criteria for clinical accuracy (Fig. 4). There were moderate positive
299 correlations between paired measurements from the PBGM and the Sof-
300 sensor (rho=0.67, P<0.0001) and between paired measurements from the
301 PBGM and the Enlite-sensor (rho=0.69, P<0.0001).

4. Discussion

This study compared pharmacodynamics of PZI and insulin degludec in healthy cats. Marked biochemical hypoglycemia and weakness occurred with both insulin formulations in all tests, when the glucose lowering effect was achieved. Vomiting was limited to three cats receiving the highest dose of PZI and to one cat receiving the highest dose of insulin degludec.

Both types of insulin had a similar onset of action, time to glucose nadir and glucose nadir. Median duration of action was significantly longer for insulin degludec than for PZI at 0.1 and 0.2 IU/kg. The differences between two insulins at 0.3 IU/kg was not significant. However, the duration of action was about 1.5 times as long for insulin degludec than for PZI at all dose levels. The duration of action of PZI was shorter than 12 h in all cats irrespective of the doses. This differed from results of a recent study, in which PZI had a duration of action exceeding 12 h in some of the treated diabetic cats, and was therefore considered potentially useful for once-a-day treatment (Ward and Louviere, 2015). Longer duration of action of PZI in the mentioned study could be explained by the applied insulin dose (0.5 IU/kg or higher). In our study, higher insulin dose was not associated with longer duration of action most likely due to rebound effect from hypoglycemia. In contrast to PZI, duration of action of insulin degludec was ≥12 h in the most cats irrespective of the doses. These preliminary data justify a study on the use of insulin degludec as once-a-day treatment in diabetic cats.

Another objective of this study was to evaluate the CGSM iPro2 with the Sof-sensor and the Enlite-sensor. From a technical standpoint, the process of initialization of the iPro2, its calibration, and the range of glucose concentrations measured were similar to the real-time CGMS previously validated by our group (Moretti et al., 2009; Moretti et al., 2010; Hafner et al., 2013). Sensor insertion was straightforward, and the implanted sensor did not adversely affect cat's well-being. A unique feature of the CGSM iPro2 is that it allows for continuous glucose monitoring in cats in a home setting, which is a considerable advantage over the currently used real-time CGMSs that require the presence of a digital recorder in close proximity to the sensor. Therefore, the use of iPro2 might be recommended for cats with poor controlled DM, or if stress-induced hyperglycemia, rebound hyperglycemia, or large glycemic variability are suspected.

The Sof-sensor was more reliable with regard to the initial glucose readings; all 20 placed Sof-sensors but only 13/17 Enlite-sensors successfully initiated glucose measurements after placement. Moreover, 17/20 Sof-sensors but only 6/13 Enlite-sensors recorded glucose data during the entire 7-day study period. Of note, 4/13 Enlite-sensors recorded glucose data <50% of the study period. Despite the overall superior performance of the Sof-sensor, the Enlite-sensors had numerically fewer interruptions of <1 h in glucose recording than the Sof-sensors; however, we considered occasional short interruptions in glucose recording of minor importance from a clinical standpoint, because they do not affect the interpretation of glucose curves in a significant way. Interruptions in glucose measurements

may occur with either sensor if they are not properly hydrated or regularly calibrated. Even slight changes in the position of the sensor caused by strain on the recorder or the overlying skin can temporarily interrupt measurements. The Enlite-sensor is thinner and shorter than the Sof-sensor and therefore might be more susceptible to interruptions. Taken together, our results suggest that the Sof-sensor is better suited to generate glucose curves in cats than the Enlite-sensor.

Both sensors yielded similar and relatively good analytical accuracy based on correlation analysis but did not completely fulfil the ISO criteria. In fact, at glucose concentrations <5.5 mmol/L, both sensors had an analytical accuracy of 90%, which is below the required 95%, and at glucose concentrations ≥5.5 mmol/L, the analytical accuracy of the Sof-sensor and Enlite-sensor was 43% and 50%, respectively, both considerably lower than the required 95% accuracy. However, the present study involved healthy cats and focused on hypoglycemia and thus the number of glucose readings ≥5.5 mmol/L was low. Including diabetic cats in future studies will aid in evaluation of the analytical accuracy of these sensors for glucose readings ≥5.5 mmol/L.

Clinical accuracy was evaluated by error grid analysis and was 100% for both sensors in the hypo- and normoglycemic ranges. According to ISO criteria, good clinical accuracy is achieved when at least 99% of glucose measurements fall within zones A and B of the consensus error grid coordinates, which occurred with both sensors in all cats.

372 The study has some limitations. First, it was performed in a small number of
373 healthy young cats, and it might not reflect the effect of tested insulin
374 formulations in older diabetic cats. Sensor glucose readings are affected by
375 the hydration status of the subcutaneous fat, and it might be possible, that
376 the reliability and accuracy of the Sof-sensor and the Enlite-sensor are
377 adversely affected in older diabetic cats with compromised hydration.
378 Second, the method used in the study to assess pharmacodynamic
379 parameters of two insulin formulations is inferior to a isoglycemic clump
380 method, which has been considered as a gold standard for the study of
381 pharmacodynamics of insulin in people (Heise and Pieber, 2007; Gilor et
382 al., 2010). Traditional blood glucose curves display the effects of exogenous
383 insulin, endogenous insulin, glucagon, and stress hormones. Following
384 severe hypoglycemia, a return of glucose to baseline reflects not only the
385 diminishing effect of exogenous insulin, but could also be the result of
386 activation of glucagon and stress hormones. In few cases (both insulin
387 formulations, data not shown), we recognized a return of glucose
388 concentration to baseline followed by another decline to a smaller degree as
389 before. These could represent counter-regulatory response that masks the
390 effect of exogenous insulin. However, it could also represent physiological
391 glucose fluctuations. It is possible, that pharmacodynamic parameters of
392 both insulin formulations were underestimated due to activation of glucagon
393 and stress hormones. However, we assume, that the counter-regulatory
394 response in cats was similar with both insulin formulations, and
395 pharmacodynamic parameters could be easily compared. Third, we used

396 insulin syringes to inject small amounts of insulin (0.5 – 1.5 IU). Insulin
397 syringes are known to be inaccurate and imprecise at doses lower than 5 IU
398 (Keith et al., 2004).
399 Fourth, the blood glucose was measured with PBGM and not with a routine
400 chemistry analyzer. However, the PBGM AlphaTRAK is specially designed
401 for use in pets. It was evaluated by different research groups, and was
402 shown to be precise and accurate at low, normal and high glucose levels;
403 glucose concentrations measured by AlphaTRAK did not significantly
404 deviate from the reference method (Cohen et al., 2009; Zini et al., 2009).

5. Conclusions

Pritamine zinc insulin and insulin degludec are well tolerated by healthy cats and cause similar degrees of hypoglycemia. Insulin degludec showed longer duration of action than PZI. Further studies on the use of insulin degludec in diabetic cats might be recommended. The CGMS iPro2 with the Sof-sensor or the Enlite-sensor is well tolerated by healthy cats. Both sensors provide good clinical accuracy but analytical accuracy does not reach the minimum set by ISO 15197:2013. The Sof-sensor seems more suitable for use in cats than the Enlite-sensor, because it produces initial glucose readings more reliably and has a better potential to generate glucose curves. However, pharmacodynamics of insulin degludec, and CGMS iPro2 need to be investigated in a larger population of diabetic cats.

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Conflict of interest

Claudia Reusch has a consultancy agreement with Boehringer Ingelheim Vetmedica GmbH.

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