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Use of an implantable pump for controlled subcutaneous insulin delivery in healthy cats

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ABSTRACT

The aim of this study was to examine the safety and reliability of a research-grade implantable pump for controlled delivery of insulin glargine in cats. For this purpose, a small telemetrically controlled drug delivery pump with a refillable reservoir was implanted into the subcutaneous tissues of the dorsal neck in 10 clinically healthy cats. The reservoir was filled with insulin glargine, and the pump was programmed to deliver four boluses of 0.25 IU/kg, 2–3 weeks apart. As a control, insulin glargine (0.25 IU/kg) was injected SC. Blood glucose and plasma insulin glargine concentrations were measured before each bolus and SC injection and for 8 h afterward. Cats were monitored for signs of discomfort.

Pumps were easily implanted and well tolerated by all cats. The experiment was completed in five of 10 cats. In four, the pump failed because of technical reasons; another cat developed severe hypoglycaemia attributable to insulin leakage. Overall, plasma insulin glargine increased after six of eight (75%) initial boluses and after one of 16 (6%) successive boluses. Glucose decreased after seven of eight (88%) initial boluses and after four of 16 (25%) successive boluses. Only the first bolus significantly increased plasma insulin glargine ($P = 0.008$) and decreased glucose ($P = 0.008$). Of 20 SC injections, 10 (50%) increased plasma insulin glargine ($P < 0.001$) and 12 (60%) decreased glucose ($P < 0.001$). The pump did not cause discomfort in cats, but life-threatening hypoglycaemia occurred in one. Frequent device problems suggest that the pump needs improvements. Because successive boluses did not increase plasma insulin glargine, this type of insulin may not be appropriate with the pump.

Introduction

Management of diabetes mellitus (DM) in cats is mostly accomplished by SC insulin injections (Reusch, 2010). However, for a substantial number of cat owners, injecting insulin in cats is challenging because of difficulty in restraining the cat, lack of time, or aversion to injections (Niessen et al., 2010). Therefore, methods other than SC injection might be beneficial in cats.

Insulin pumps have been developed to simplify the treatment of human diabetics. They may be external or implantable but external pumps are most frequently used. External pumps have a display that allows the user to enter dosage information. Most external pumps deliver insulin through a cannula inserted into the subcutaneous tissues; a separate hand-held controller is used to adjust rates (Reznik and Cohen, 2013).

Implantable pumps have been limited to humans with type 1 DM in which an external pump failed to achieve acceptable glycaemic control. These pumps are surgically implanted into the subcutaneous tissue and insulin is delivered into the peritoneal cavity via a catheter. Insulin delivery is remotely controlled with a pump communicator (Haveman et al., 2010).

Studies have shown that the use of external or implantable insulin pumps provides superior glycaemic control compared to multiple daily SC insulin injections in humans with DM (Pickup, 2012; Reznik and Cohen, 2013).

To date, insulin pumps have not been used in cats. External pumps appear unsuitable because they need to be attached to the cat with a bandage. Implantable pumps might be more practical and could provide cat owners with a method that eliminates restraint and the need to inject insulin. Therefore, the aim of this feline study was to evaluate a research-grade implantable pump to wirelessly deliver SC insulin. The ease of implantation, long-term tolerance, and the ability of the pump to reliably deliver insulin were assessed in clinically healthy cats.

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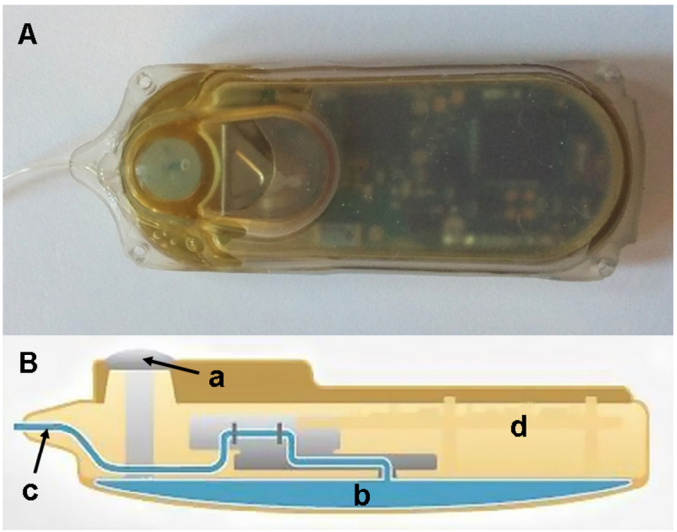

Fig. 1. (A) Implantable pump for SC delivery of insulin glargine in cats; the pump weighs 5.2 g and has a total volume of 3.7 cm^3, a length of 42 mm, a width of 16 mm and a thickness of 7 mm. (B) Structure of the pump. (a) The convex septum can be pierced with a needle multiple times to refill the 1 mL-expandable reservoir at the bottom (b), increasing pump thickness up to 11 mm when full. (c) Through a 0.5 cm-long catheter with outer diameter of 1 mm drugs are delivered into the subcutaneous tissue at a constant rate, as single or periodic boluses; the flow rate varies from 0 to 100 μL/h with a variability of <5%. (d) Electronic components and moving parts of the pump. The drug dosage and exact timing are programmed on a separate wireless portable computer, which sends the information to the pump. Once programmed, drug delivery by the pump is automatic and handling of the animal is not required. The maximum battery life is 8 months.

Materials and methods

Pump

Because implantable pumps for humans are too large for cats, a small implantable pump (ithetis,[1] Antlia), developed to deliver drugs in laboratory animals for preclinical studies, was used (Fig. 1, pump details).

Insulin glargine stability

Insulin glargine (Lantus, Sanofi Aventis) was used in the pump. Storage recommendations stated that unopened insulin glargine cartridges should be refrigerated at 2–8 °C and, if protected from direct heat and light, also at room temperature for 28 days.[2] However, there is no information on their storage at higher temperatures or for longer periods. Therefore, the stability of insulin glargine was assessed. An insulin glargine cartridge was wrapped in plastic and aluminium foil for light protection and placed in an agitator at 37 °C for 8 weeks. At the beginning of the stability test and then every 2 weeks for 8 weeks, an insulin glargine aliquot was collected and purified by reversed-phase high-performance liquid chromatography. Insulin glargine was then analysed with matrix-assisted laser desorption/ionisation using time-of-flight (MALDI-TOF) mass spectrometry in linear and reflection modes.

Animals and pump implantation

Ten, 2-year-old, male, domestic-shorthair cats with a median bodyweight of 5.0 kg (range, 4.5–5.6) were enrolled; they were healthy based on physical examination, complete blood cell count and serum biochemical profile. To verify that the pump was functioning after filling and immediately before surgical implantation, we determined whether the computer recognised the pump and programmed the delivery of a bolus. The pump was implanted SC in the dorsal neck and removed at the end of the experiment, 90 days later. For implantation, a 3 × 5 cm area of skin was clipped and disinfected. Under short general anaesthesia, a 1.5 cm skin incision was made and a 3 cm subcutaneous pouch was created to accommodate the pump, with the reservoir positioned dorsally. The pump was secured to the subcutaneous tissue with two non-absorbable sutures and the skin was sutured with four sutures which were removed after 1 week. After implantation, cats were monitored twice daily during the first week for discomfort (pruritus, vocalisation, pain during neck palpation, increased respiratory rate), local and systemic signs of inflammation (erythema, erosions, bleeding, purulent discharge, increased rectal temperature, lethargy, anorexia). Subsequently, cats were monitored daily until the study end and for 1 week after pump removal.

The pumps were removed at the study end under anaesthesia. The pouch was visually inspected to identify signs of inflammation or abscess formation; the integrity and functionality of the pump were confirmed grossly and by programming a bolus, respectively. Antimicrobial drugs were not administered during any procedure. The study was approved by the Veterinary Office of the Canton Zurich, Switzerland, with amendment on 27 May 2013 (Approval No. 69/2011).

Filling of the pump, pump boluses and SC injections of insulin glargine

The pump reservoir was filled with 1 mL of insulin glargine before implantation and 30 days later using a 1 mL syringe with a 28-gauge needle. Cats were sedated during reservoir refilling. Any remaining insulin was removed from the reservoir transcutaneously prior to refilling with new insulin glargine.

Insulin glargine boluses were scheduled after 1 day and for 3 weeks after pump implantation and after 1 and 4 weeks from pump refill. A bolus consisted of 0.25 IU/kg of insulin glargine, which has been shown to induce moderate-to-severe hypoglycaemia in healthy cats (Marshall et al., 2008). To confirm that the insulin boluses lowered blood glucose concentrations, the cats served as their own controls by receiving SC injections of insulin glargine (0.25 IU/kg); injections were given 1 week and 4 weeks after pump implantation and 1 day and 3 weeks after pump refill. The timing of injections was arbitrarily chosen to mirror that of boluses. All boluses and injections were administered at 8:00 am to non-sedated cats. Glucose concentrations were measured by collecting capillary blood from the ear as previously described (Zini et al., 2009), just before each bolus and injection (baseline), and 1, 3, 5, 7, and 9 h later. At each time point, a blood sample was also collected by jugular venipuncture to measure plasma insulin glargine concentration. Pumps were removed after 90 days.

To reduce the risk of severe hypoglycaemia (blood glucose <36 mg/dL) induced by insulin glargine, cats were offered an amount of food (DM, Purina) that constituted approximately one third of their daily requirements. Once the cat started eating, the insulin glargine bolus or the SC injection was given. An additional meal or IV glucose was provided if severe hypoglycaemia developed. Cats that developed severe hypoglycaemia for >1 h were withdrawn from the study.

Assay to measure insulin glargine in cat plasma

Insulin glargine was quantified in EDTA-plasma with an ELISA developed for humans (Glargine ELISA, Invitron). To verify whether the assay measured insulin glargine in cat plasma, blood samples from three other clinically healthy cats and three cats with DM treated with insulin glargine were used. Assay validation included calculation of recovery and linearity (Appendix A: Supplementary material).

Five clinically healthy cats that had never received insulin glargine were used to verify that the insulin glargine ELISA did not cross-react with feline insulin. The cats were fed a high-energy meal (Recovery, Royal Canin) at approximately 9:00 am. The meal met the complete daily requirements and was given to stimulate endogenous insulin secretion. Blood was collected at 8:30 (before meal), 9:30, 10:15, and 11:00. Blood samples were used in the insulin glargine ELISA to measure plasma insulin; a post-meal increase in plasma insulin suggested that the assay cross-reacted with feline insulin. Feline insulin was also measured in the same samples using a cat-optimised ELISA (Feline Insulin ELISA, Mercodia) to confirm that the meal increased endogenous insulin; the assay has been previously validated for measuring endogenous insulin in cats (Strage et al., 2012).

Statistical methods

To assess whether the meal promoted endogenous insulin secretion in the five clinically healthy cats as measured with the cat-optimised ELISA, the Wilcoxon matched-pairs test was used to compare basal and peak insulin concentrations; the test was also used to analyse the results of the plasma insulin glargine ELISA to exclude cross-reactivity. Differences in plasma insulin glargine and capillary blood glucose concentration before and after pump bolus delivery and SC injection were analysed as above by comparing peak and nadir values with basal concentrations, respectively. An insulin peak was defined as noticeably increased when it was above the baseline value by >50%. A glucose nadir was defined as noticeably decreased if it was below the baseline value by >30%. Furthermore, for boluses and SC injections that resulted in a noticeable increase in plasma insulin glargine, time-to-peak was compared using the Mann–Whitney U test. Differences were considered significant at $P < 0.05$.

Results

Insulin glargine stability

MALDI-TOF mass spectrometry demonstrated structural stability of insulin glargine over the 8-week testing period (Appendix A: Supplementary material).

[1] See: ithetis Implantable Drug Delivery Devices. http://www.ithetis.com (accessed 1 December 2016).

[2] See: Lantus SoloSTAR. http://www.lantus.com/starting/how-to-use/store-lantus (accessed 1 December 2016).

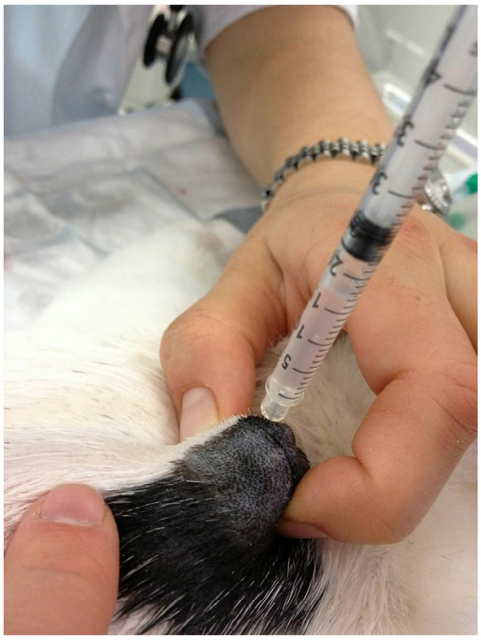

Fig. 2. Before the pump is refilled with insulin glargine 30 days after implantation, the reservoir is emptied using a 1 mL syringe. The needle is pushed through the skin and the convex septum of the reservoir.

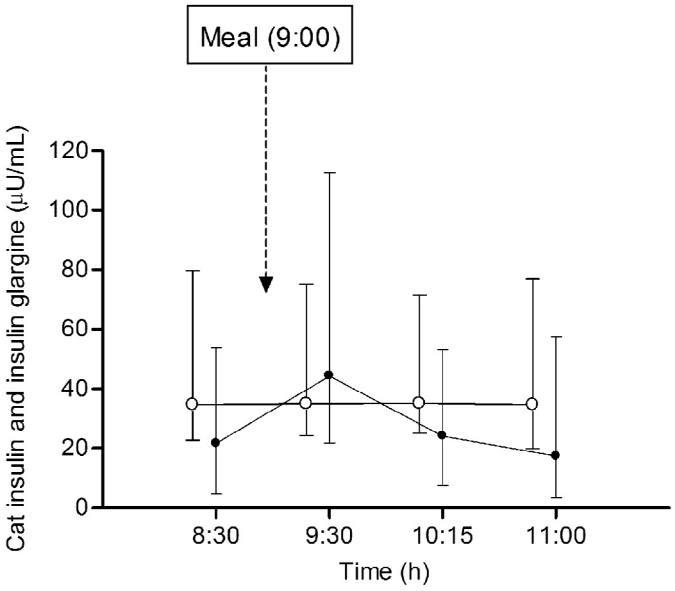

Fig. 3. Plasma concentrations (median and interquartile range) of feline insulin (cat-optimised ELISA, black dots) and insulin glargine (insulin glargine ELISA, open circles) in cats fed a meal (at 9:00) that met the daily energy requirement. A significant post-prandial insulin peak was detected with the cat-optimised ELISA ($P = 0.043$) but not with the plasma insulin glargine ELISA ($P = 0.813$).

Implantation, animal wellbeing, and pumps

Pump implantation took 25–30 min. In nine (90%) of 10 cats, the pumps were removed after 90 days. One cat developed severe hypoglycaemia (blood glucose 20 mg/dL) within 6 h of implantation. The pump was removed immediately. Leakage of insulin from the convex septum of the reservoir was identified. The cat recovered after glucose infusion and was withdrawn from the study.

The remaining nine cats did not have detectable signs of discomfort or inflammation; wellbeing, appetite, and rectal temperature were normal throughout the study. The skin and subcutaneous tissues nearby the pump and entire pouch appeared normal at pump removal. At removal, no visible changes were seen in the pumps; patency of the catheter and integrity of the convex septum were preserved.

Pump boluses and refill, SC injections of insulin glargine

Before implantation the pumps were recognised by the computer and programming of a bolus generated a drop of insulin from the catheter tip in each case, as expected. Delivery of the drop was accompanied by a faint buzzing noise from the pump; the noise lasted 5 s and the cats did not react to it.

In one cat, the computer failed to recognise the pump and therefore boluses of insulin glargine were not delivered; the pump was removed at the study end (90 days). In the remaining eight cats, no problems were encountered during the first bolus. The second bolus programmed 3 weeks later failed in two cats because the computer command was not received or processed by the pump; the pumps were removed 90 days later. In the remaining six cats, the second bolus was delivered without incident.

The pump reservoir in the remaining six cats was refilled 30 days after implantation. The convex septum was palpated through the skin and the insulin injected with a syringe (Fig. 2). This procedure took 1 min, required only brief sedation and was straightforward.

The third bolus was programmed 1 week after refill and failed in one cat because the computer command was not received or processed by the pump; in this cat the pump was removed 90 days later. The third bolus was delivered 1 week after refill in five of six cats. The fourth bolus was programmed and processed in the same five cats 4 weeks after refill. Hence, five (50%) of 10 cats successfully completed the study. No problems were encountered with SC injection of insulin glargine; if administration of boluses was not successful, the next injections were not provided.

Insulin glargine in cat plasma and capillary blood glucose

The insulin glargine ELISA was suitable for measuring insulin glargine in cat plasma, yielding a recovery rate of 98–108% and a linearity of 99–110%. There was no evidence of cross-reactivity between the insulin glargine ELISA and feline insulin. By comparing post-meal peak to fasting concentration, we demonstrated that the high-energy meal increased endogenous insulin in all five cats based on the cat-optimised ELISA ($P = 0.043$). An analogous post-meal increase in insulin was not detected with the insulin glargine ELISA ($P = 0.813$; Fig. 3).

Six (75%) of the eight initial boluses led to noticeable plasma insulin glargine peaks accompanied by decreased capillary blood glucose (Fig. 4). Two boluses (25%) did not result in a noticeable increase in plasma insulin glargine; one of these was associated with a decrease in capillary blood glucose and the other was not. By comparing post-bolus peak and nadir to baseline, we demonstrated that the first bolus was associated with a significant increase in plasma insulin glargine ($P = 0.008$) and decreased capillary blood glucose ($P = 0.008$), respectively. Of the six second boluses, one (17%) increased plasma insulin glargine noticeably and the remaining five (83%) did not. Capillary blood glucose decreased noticeably in only one cat, which had a plasma insulin glargine peak >47% than baseline. By comparing post-bolus peak and nadir to baseline, it was shown that the second bolus did not significantly increase plasma insulin glargine ($P = 0.098$) or decrease capillary blood glucose ($P = 0.063$), respectively.

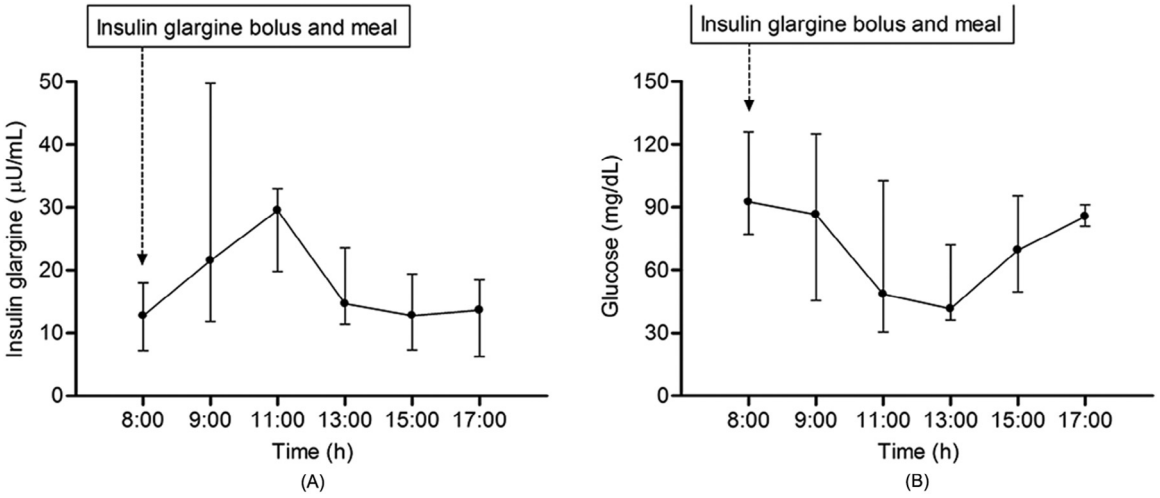

Fig. 4. Plasma concentrations (median and interquartile range) of (A) insulin glargine and (B) capillary blood glucose in six cats after pump delivery of the first insulin glargine bolus. A plasma insulin glargine peak and a temporary decrease in glucose concentration occurred in all six cats.

Five cats had a third bolus delivered 1 week after refill and a fourth bolus 4 weeks after refill. None of these 10 boluses caused a noticeable rise in plasma insulin glargine. In three cases, an insulin peak <10% higher than baseline was associated with a noticeably decreased capillary blood glucose (two cats with the third bolus, one cat with the fourth bolus). Overall, the third and fourth boluses did not significantly affect plasma insulin glargine and capillary blood glucose.

Of the 20 SC insulin glargine injections, 10 (50%) led to a noticeable increase in plasma insulin glargine, seven (35%) led to an increase of 25% to <50%, and three (15%) led to an increase of <25%. Twelve injections (60%) caused a noticeable decrease in capillary blood glucose concentration, four (20%) a decrease of 15 to <30%, and four (20%) a decrease of <15% relative to baseline. By comparing post-injection peak and nadir to baseline, it was shown that SC insulin glargine injections significantly increased plasma insulin glargine ($P < 0.001$) and decreased capillary blood glucose ($P < 0.001$; Fig. 5), respectively.

For boluses that led to a noticeable increase in plasma insulin glargine, the median time-to-peak was 3 h (range, 1–3 h) and for SC injections the median time-to-peak was 3 h (range, 1–5 h); time-to-peak did not differ between boluses and SC injections ($P = 0.633$).

Discussion

Pump implantation was quick and easy, and the device was well tolerated by all cats. However, haematoma, cutaneous erosion, pain or infection at the surgical site has been reported to occur in approximately 10–17% of people with type 1 DM treated with implantable pumps (Haveman et al., 2010; van Dijk et al., 2012).

Nine of the 10 pumps were intact on gross inspection after removal, but one was faulty and leaked insulin from the convex septum, resulting in severe hypoglycaemia. Because hypoglycaemia is a serious complication of insulin administration and because the septum should tolerate repeated perforations, efforts should be focused to modify the robustness of the material used for the septum. In three studies of 160 human diabetics treated with an implantable pump, only one person experienced severe hypoglycaemia because of structural defects (Gin et al., 2003; Haveman et al., 2010; van Dijk et al., 2012).

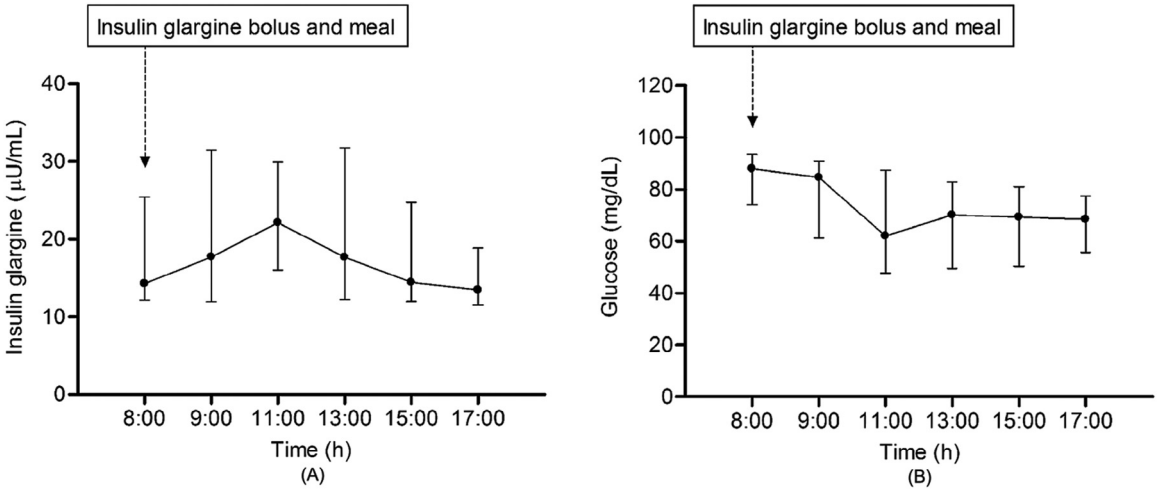

Fig. 5. Plasma concentrations (median and interquartile range) of (A) insulin glargine and (B) capillary blood glucose concentration after SC injection ($n = 20$) of insulin glargine in cats. Overall, the insulin glargine concentration significantly increased and glucose concentration decreased (both $P < 0.001$).

Before implantation, all pumps were recognised by the computer and produced the programmed drop of insulin; after implantation, however, one of nine pumps was not recognised by the computer. Analogous failures happened at the time of the second and third boluses in a further three pumps. Thus, only 50% of pumps delivered all four programmed boluses. The reasons for these failures are unclear. There were no signs of catheter tip obstruction in the non-functional pumps. It was therefore assumed that problems involved the pump hardware. In human diabetics treated with implantable pumps, technical failures leading to replacement have been documented in 5–17% of patients (Haveman et al., 2010; van Dijk et al., 2012). Refill of the pump reservoir was straightforward in all cats, but the procedure was performed under sedation. Without sedation, refill might be difficult in fractious cats.

The administration of insulin glargine via the pump increased plasma insulin glargine to a noticeable degree in 75% of the first boluses, in only 17% of the second boluses and in none of the remaining boluses; increases in plasma insulin glargine were only statistically significant for the first bolus. Because the computer and pumps appeared to be functional until the end of the study, it is possible that failure was related to insulin glargine stability over time. Mass spectrometry demonstrated that in-vitro degradation and aggregation of insulin glargine were likely to be negligible. However, it is possible that changes in the three-dimensional conformation of the protein were responsible for the malfunction, because conformational changes might not be detected by mass spectrometry (Villanueva et al., 2002). For in-vitro testing, insulin glargine was incubated in its cartridge and not in the pump; it is therefore possible that the materials of the reservoir affected the stability of the insulin. The absence of an increase in plasma insulin glargine concentration was largely accompanied by an absence of a noticeable decrease in capillary blood glucose. Interestingly, none of the third boluses produced an increase in plasma insulin glargine or a decrease in capillary blood glucose even though the reservoir was emptied before refill with fresh insulin glargine after the second bolus. This suggests that insulin glargine was rapidly inactivated in the pump, possibly by residues from the first filling or by a pH change. In contrast to the results of our study, a semisynthetic human analogue insulin that had surfactant added for long-term stability was used successfully in human diabetics with an implantable pump (Haveman et al., 2010). However, the pharmacodynamics of this insulin is unknown in cats and at the time of the study the insulin product was not commercially available.

Subcutaneous injection of insulin glargine caused a significant increase in plasma insulin glargine and a significant decrease in capillary blood glucose, but both of these changes occurred together in only approximately 50% of cats. A slight modification of the arbitrary criteria used to define a change as 'noticeable' (plasma insulin glargine peak exceeding baseline by ≥25%; value of glucose nadir below baseline by ≥15%) would have raised this proportion from 50% to 85%. It is not clear why all injected cats did not have a noticeable increase in plasma insulin glargine, but it is possible that in some, absorption from the injection site was relatively slow. Furthermore, the high-energy meal fed to the cats at the time of insulin glargine injection to prevent severe hypoglycaemia may have decreased the glucose-lowering effect of the insulin.

Of note, the time-to-peak of plasma insulin glargine was 3 h and did not differ between pump boluses and SC injections. This means that pumps that were still functional delivered insulin pulses into the subcutaneous tissues as SC injections.

This study was limited by the small number of cats that received all boluses of insulin glargine and the relatively short period of time the pumps were implanted. Furthermore, multiple sources of error, related either to the pump or to the type of insulin used, made the interpretation of results difficult. Importantly, the use of long-acting insulin preparations might not represent an optimal therapeutic solution in diabetic cats with implantable pumps. Failure of accurate delivery of long-acting insulin by pumps would be dangerous, whereas similar problems could be more easily corrected if a short-acting insulin preparation was used.

Conclusions

The insulin delivery pump did not cause discomfort in cats, but caused life-threatening hypoglycaemia in one cat. Frequent device problems indicate that technical improvements are necessary prior to the initiation of subsequent studies. Because successive boluses did not increase plasma insulin glargine, this insulin type may not be appropriate for use with the insulin pump.

Conflict of interest statement

Antlia supplied the implantable pump used in this study. None of the authors of this paper has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Appendix: Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tvjl.2016.12.006.

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