Efficacy and safety of porcine insulin zinc suspension (IZS-P) for reducing hyperglycemia and associated clinical signs in cats with diabetes mellitus

Philippe Brianceau[1*], Ted Chester[1], Allyson Smith[1], Linda Horspool[2] & David Laxton[1]

[1]Intervet Inc, 29160 Intervet Lane, Millsboro, DE 19966-0318. *philippe.brianceau@sp.intervet.com
[2]Intervet International bv, International Marketing, PO Box 31, 5830 AA Boxmeer, The Netherlands

Abstract

An open, unmasked study was conducted to provide substantial evidence of the clinical effectiveness and safety of porcine insulin zinc suspension (IZS-P, Vetsulin®) for reducing hyperglycemia and its associated signs in cats with diabetes mellitus. The study was conducted in the US in accordance with the current FDA, CVM and VICH Guidance on Good Clinical Practice.

Cats were enrolled based on elevated fasting blood glucose (>250 mg/dL on two occasions) with concurrent glycosuria and clinical signs of diabetes mellitus. Cats that met specified criteria on prior treatment or with coexisting primary diseases were excluded. A baseline blood glucose curve (Day 0) was completed and IZS-P therapy (approximately 1 to 2 IU per subcutaneous injection q 12 h) initiated. Glucose curves and clinical signs were re-evaluated on Days 7, 14, 30, 60 and 180 and the dose was adjusted accordingly. Overall response to treatment in each cat was recorded on a visual analogue scale (VAS). Additional examinations to assess the long-term safety were carried out at 90, 120 and 150 days. Complete blood count (CBC) and serum chemistry were performed during the course of the study and urinalysis prior to enrollment.

Mean VAS score decreased from 93.8 mm on Day 0 to 31.2 mm and 25.0 mm on Days 60 and 180, respectively (p<0.001 both days). This was mirrored by a substantial reduction in polyuria, polydipsia and polyphagia. Mean blood glucose decreased from 394.1 mg/dL on Day 0 (n=77) to 216.7 mg/dL (n=76) and 219.5 mg/dL (n=73) on Days 60 and 180, respectively (p<0.001 both days). Mean glucose nadir decreased from 343.3 mg/dL on Day 0 to 145.7 mg/dL and 155.9 mg/dL on Days 60 and Day 180, respectively (p<0.001 both days). Blood glucose was <300 mg/dL in 5.2%, 75.0% and 71.2% of the cats and blood glucose nadir <200 mg/dL in 0%, 72.4% and 69.9% of the cats on Days 0, 60 and 180, respectively. Mean fructosamine concentration decreased from 604.3 µmol/L on Day 0 to 451.3 µmol/L and 448.4 µmol/L on Days 60 and 180, respectively (p<0.001 both days). Diabetes remission occurred in four cats. Less than 3% (2/77) of the cats failed to respond to treatment.

Hypoglycemia (blood glucose concentration <50 mg/dL) was reported as an adverse event associated with clinical signs (lethargy, diarrhea, decreased appetite/inappetence, vomiting, and/or hypothermia) in 16.7% (13/78) of the cats. Biochemical hypoglycemia (blood glucose concentration <50 mg/dl) without clinical signs was observed in 51 cats at some time during the study. Polyneuropathy was documented in 5.1% (4/78) of the cats. Two injection site reactions were reported (mild bruising at the injection site, mildly thickened subcutis). These results confirm that IZS-P is effective and safe for reducing hyperglycemia and its associated clinical signs in cats with diabetes mellitus.

Introduction

Porcine insulin zinc suspension (IZS-P) was first approved for use in the early 1990s (Caninsulin®, Intervet International bv, The Netherlands) and is registered for dogs and cats as Caninsulin® in more than 30 countries. IZS-P is safe and effective in cats when dosed appropriately and well monitored.[1,2]
This multi-center, historical control, unmasked clinical study was conducted to provide substantial evidence of effectiveness and safety of porcine insulin zinc suspension (IZS-P, Vetsulin®) in cats with diabetes mellitus.[3] The effect of IZS-P therapy on reducing hyperglycemia and hyperglycemia- associated clinical signs was evaluated.
The study was conducted in the US in accordance with CVM[a], and VICH[b] Good Clinical Practice Guidance.

a Center for Veterinary Medicine
b International cooperation on harmonization of technical requirements for registration of veterinary medicinal products

Materials & Methods

Study design

- Multi-center, historical control, unmasked clinical study
- No negative controls due to the nature of the disease
- Clinical signs, blood glucose concentrations, and fructosamine were compared before and after IZS-P treatment initiation.

Inclusion criteria

- Two fasting blood glucose measurements >250 mg/dL, and
- Glycosuria, and
- One or more of the following clinical signs: Polyuria, polydipsia, polyphagia, weight loss despite good appetite, ketonuria (without signs of severe ketoacidosis)

Exclusion criteria

- Treatment with another insulin for longer than 1 week
- Presence of
  - clinical signs of severe ketoacidosis
  - significant concomitant disease: hyperthyroidism, active pancreatitis, hyperadrenocorticism, acromegaly, major organ failure, major infection
- Treatment with
  - insulin or oral hypoglycemic agents within 48 ho
  - long-acting corticosteroids or progestagens within 45 days of enrollment.
  - other medications that could interfere with diabetes treatment

Feed, water and exercise

- Food that could substantially influence the response to insulin therapy (e.g. semi moist foods, diabetic diets) was contraindicated in the first 60 days of the study.
- Feeding and water recommendations:
  - Free fed cats were offered food *ad libitum*
  - Cats routinely portion fed could be fed 50% of their daily ration twice a day at the time of insulin treatment
  - Water was available *ad libitum*
- Exercise was kept consistent

Study Time	Activities
Day 0	1. Baseline blood glucose curve. 2. Diabetes control evaluation. 3. IZS-P therapy initiation either immediately following the baseline glucose curve (Day 0) or on the day following the curve. 4. Blood glucose spot checks approximately 4 and 8 hours after first IZS-P dose.
Between Day 0 and 7	Laboratory test results evaluation by Investigator (If not done prior to Day 0).
Day 7 ± 2 days & Day 14 ± 2 days	1. Physical examination. 2. Clinical sign assessments. 3. Blood glucose curve. 4. Diabetes control evaluation. 5. IZS-P dose adjustment.
Day 30 ± 5 days & Day 60 ± 5 days	1. Physical examination. 2. Clinical sign assessments. 3. Blood glucose curve 4. Diabetes control evaluation. 5. IZS-P dose adjustment. 6. CBC, serum chemistry, and fructosamine.
Approximately Day 90, 120, and 150	1. Physical examination. 2. Clinical sign assessments.
Approximately Day 180	1. Physical examination. 2. Clinical sign assessments. 3. Blood glucose curve. 4. Evaluate diabetes control. 5. Adjust IZS-P dose if necessary. 6. CBC, serum chemistry, and fructosamine.

Starting insulin treatment

- Starting dose: 1 to 2 IU IZS-P twice daily by subcutaneous injection, 2 to 5 cm from the dorsal midline, varying from behind the scapulae to the mid-lumbar region, alternating sides at each injection

Dose adjustment

- Dose was adjusted based on
  - Clinical signs
  - Glucose curves and laboratory results

Satisfactory dose

- Elimination or reduction of clinical signs to the satisfaction of the cat owner
- Cat maintained or attained appropriate weight
- Acceptable findings at physical examination
- Acceptable blood glucose values

Evaluation of efficacy and safety

- Blood glucose curves:
  - Venous blood samples were taken before and at 2, 4, 6, 8 and 10 hours after insulin injection.
  - Blood glucose was determined using a hand-held glucometer[c].
- Diabetes control evaluation:
  Overall response to treatment of each cat was recorded on a visual analogue scale (VAS)

Statistics

Sample size calculations were done using 95% confidence, two-sided hypotheses, and 80% power (nQuery Advisor version 3.0) based on results obtained in a pilot study of similar design. It was determined that enrolling at least 75 cats should ensure 60-70 cats reaching Day 180, providing sufficient inferential value to support substantial evidence of effectiveness and provide sufficient safety data for FDA approval.

c Accu-Chek® Advantage®, Roche Diagnostics Operations, Inc.

Results

- Primary effectiveness evaluation on Day 60: 76 cats
- Safety data
  - For cats completing Day 7 evaluation: 78 cats
    - 32% spayed female, 68% castrated male
    - 3 to 17.5 years old
    - Mainly domestic shorthair (51, 65%) (Fig. 1)
  - For 66 cats through Day 180
- Diabetes remission occurred in four cats
- Less than 3% (2/77) of the cats failed to respond to treatment

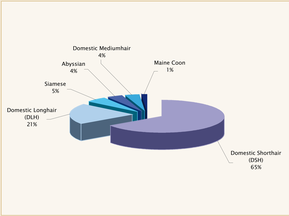

Fig. 1. Cat breeds (number,%).

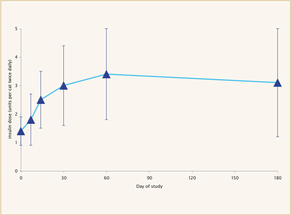

Fig. 2. Mean IZS-P dose (SD) per cat q12 h during the study.

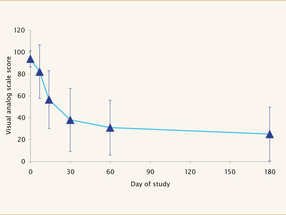

Fig. 3. Diabetes control increased (mean VAS score (SD) decreased) from Day 0 to Days 60 and 180, respectively (p<0.001 both days).

Safety

- Mild clinical signs of hypoglycemia (lethargy, diarrhea, decreased appetite/inappetence, vomiting, and/or hypothermia) were reported in 16.7% (13/78) of the cats. In all cases, the clinical signs resolved following symptomatic treatment and/or IZS-P dose adjustment.
- One cat had seizures following accidental overdosing by the owner and during the subsequent dose adjustment. The cat responded to supportive therapy and had no further hypoglycemic episodes.
- Biochemical hypoglycemia (blood glucose concentration <50 mg/dl) without clinical signs was observed in 51 cats at some time during the study.
- Polyneuropathy was documented in 5.1% (4/78) of the cats. Two cases occurred while the IZS-P dose was still being adjusted. One of these cats had practically no signs of polyneuropathy by Day 180.
- Two injection site reactions were reported (mild bruising at the injection site, mildly thickened subcutis).
- One cat died (unknown cause) and three cats were euthanized (peritonitis (1), bile duct obstruction (1), anorexia vomiting and depression (1)).

Efficacy

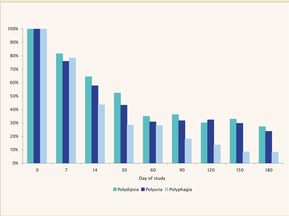

Fig. 4. Percentage of cats with polyuria, polydipsia and polyphagia decreased with treatment mirroring the significant decrease in VAS

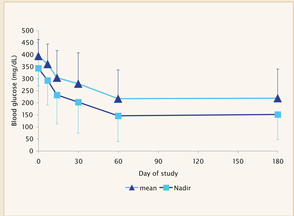

Fig. 5. Mean blood glucose (SD) and nadir blood glucose (SD) decreased significantly from Day 0 (n=77) to Days 60 (n=76) and 180 (n=73), respectively (p<0.001 both days).

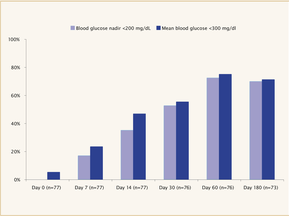

Fig. 6. Mean blood glucose decreased to <300 mg/dl and blood glucose nadir to <200 mg/dl in most of the cats.

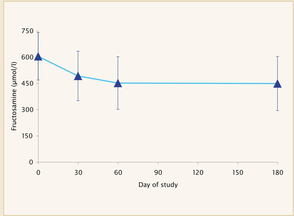

Fig. 7. Mean fructosamine concentration (SD) decreased significantly from Day 0 to Days 60 and 180, respectively (p<0.001 both days)

Summary and Conclusions

- These results confirm that IZS-P is effective and safe for reducing hyperglycemia and hyperglycemia-associated clinical signs of diabetes mellitus in cats.
- No clinical signs were observed in the majority of cases of biochemical hypoglycemia. This emphasizes the need for regular monitoring of diabetic cats receiving insulin therapy. The most common clinical sign reported during treatment was lethargy. All cats responded to supportive glucose therapy and/or a dose adjustment.

Acknowledgements

The authors are grateful to Drs. Beachy, Eilers, Buzhardt, St. Romain, Carroll, Clekis, DeBerry, Rcihter, Dole, Hackett, Bledsoe, Hodge, Jezbera, Lively, Mahanes, Meyer, Santen, Sifferman and Suska and their clients and their cats for their participation in the study.

References

1. Martin GJ, Rand JS. *Control of diabetes mellitus in cats with porcine insulin zinc suspension.* Vet Rec 2007;161:88-94.
2. Michiels L, Reusch CE, Boari A, et al. *Treatment of 46 cats with porcine lente insulin – a prospective, multicentre study.* J Feline Med Surg 2008;10: in press, doi:10.1016/j.jfms.2007.10.013.
3. Vetsulin *Freedom of Information Summary.* NADA 141-236

Intervet
Schering-Plough Animal Health