Assessment of Once Daily Dosing with ProZinc® Insulin in Diabetic Beagle Dogs

Cynthia R. Ward VMD PhD[1], Martha Winhall DVM[2], Carla Kroh DVM[3], Walt Ingwersen DVM[4], Philip Watson BVetMed[3]

[1] University of Georgia, Athens, Georgia USA [2]InterVivo Solutions Inc., Ontario, Canada [3]Boehringer Ingelheim Vetmedica GmbH, Ingelheim am Rhein, Germany [4]Boehringer Ingelheim Animal Health, Ontario, Canada

Abstract: The purpose of this study was to assess glucose control of PZI insulin (ProZinc®) given SID in dogs with laboratory-induced diabetes mellitus. The hypothesis was that ProZinc® will control hyperglycemia and clinical signs in diabetic dogs using a SID posology. Nine well-controlled diabetic dogs on twice daily lente insulin (Caninsulin®) were transitioned to ProZinc® as a single morning dose while maintaining their twice daily feeding regimen. The initial ProZinc® dose of 1U/kg was decreased to 0.4-0.5IU/kg because of asymptomatic hypoglycemia and then increased by 0.05-0.1IU/kg every 5 days as needed. Glucose control was determined by continuous interstitial glucose monitoring, glucometer, urine ketone, and fructosamine measurements. Food and water consumption, bodyweight, clinical observations, and physical exam parameters were used to assess clinical control. This was a non-randomized, non-blinded laboratory study conducted over 56 days.

ProZinc® insulin showed a clear and dose dependent biphasic glucose lowering effect over 24 hours. Onset of action was 1-2 hrs, with two peaks of activity occurring at 8-10 and 12-14 hrs. Duration of action was 20-22 hrs. At D56 average weight and water consumption was consistent with those at D0; fructosamine was slightly increased. Food consumption remained consistent. The final ProZinc® dose range was 0.45-0.8IU/kg; however, 3 dogs may have required subsequent upward adjustments. These results show a biphasic glucose lowering effect of ProZinc® over each 24-hour period, clearly demonstrating that SID dosing is appropriate when using this insulin. The starting dose should be less than 1IU/kg, but may be higher under field conditions.

Materials and Methods: This was a non-randomized, non-blinded, laboratory study including 9 Beagle dogs with chemically induced diabetes mellitus. On the first day of baseline (Day -4), subjects were acclimated to housing conditions and placement of continuous glucose monitors (CGM). A series of health screening measures including veterinary examinations, serum fructosamine analysis, hematology, clinical chemistry analysis and urinalysis were performed, deeming all subjects suitable to continue onto the trial. In addition, the following procedures were initiated: 3x daily interstitial fluid (ISF) glucose value capture via CGMs, 3x daily blood glucose (BG) measurements via glucometer, 2x daily clinical observations, daily urine output determination and daily food/water consumption measurements. During acclimation, animals were maintained on a previously established diabetic treatment regimen of twice daily Caninsulin® administration following AM and PM feed offerings. On Day -1, PM Caninsulin® doses were withheld to serve as a washout prior to initiation of ProZinc® administration the following morning. Once daily administration of ProZinc® began on Day 0 at a dose of 1 IU/kg sid. Dosing was conducted in the AM, following a food offering, and PM feeding occurred 8 hours after dosing. Starting on Day 1, doses were adjusted down or withheld as needed, to address concerns about hypoglycemia, although all dogs were clinically normal. Due to a more marked response than anticipated in several subjects, the initially planned dose of 1 IU/kg was decreased on Day 4 to 0.5 IU/kg for 8 subjects and to 0.42 IU/kg for the 9th subject. Beginning on Day 5, scheduled dose adjustments in increments of 0.1 IU/kg occurred every 5 days, as needed based on individual diabetic control. Beginning on Day 25, doses were adjusted by no more than 0.05 IU/kg and effective Day 28, downward dose adjustments of ProZinc® no longer occurred unless clinical signs of hypoglycemia were present. By this time, optimal doses for many subjects had not yet been determined and as such, the study was extended to Day 42. In an attempt to minimize the degree to which blood glucose levels continued to fluctuate, the feeding to dosing schedule was changed such that daily ProZinc® administration was timed to occur 15 minutes (vs one hour) after AM feed offering and the PM feed ration was provided 10 hours (vs 8 hours) following dosing. Lastly, to obtain a more robust data set, the study was extended until Day 56 for 6 of the 9 subjects.

Over the course of study, in addition to the daily procedures initiated at baseline, blood collections for fructosamine analysis were performed every 7 days until Day 42 and again at Day 56. Hematology and clinical chemistry analysis were conducted on Days 0, 28 and 42, urinalysis on Days 0 and 28 and veterinary examinations on Days 27 and 42. Urine Chemstrip® analysis was also conducted every 7 days until Day 42. Initially, animal body weights were measured every 7 days but beginning on Day 21, were performed on the day prior to scheduled dose adjustments. Food consumption, water consumption and urine output were determined until Day 42.

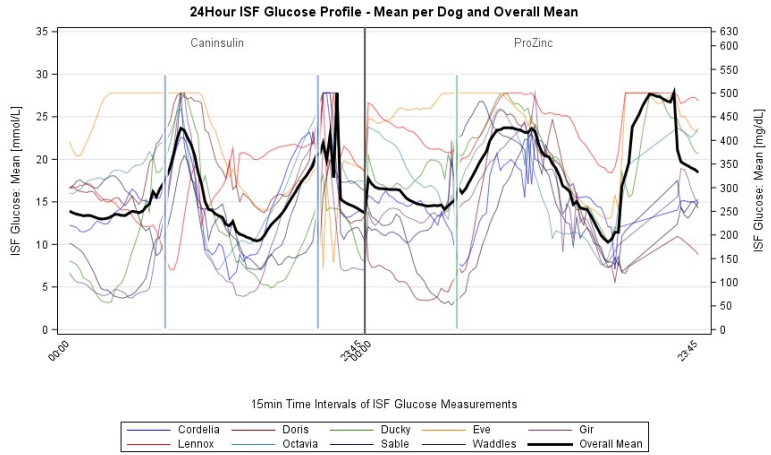

Fig 1. Continuous Interstitial Glucose Measurement. Means of interstitial fluid glucose for each dog and for all dogs from the last 3 days of Caninsulin® (left) and ProZinc® (right). Vertical purple lines indicate bid dosing for Caninsulin® and vertical green line indicates sid dosing for ProZinc® All dogs were fed bid when insulin was given. When on sid ProZinc®, dogs were given a second meal at 17:00.

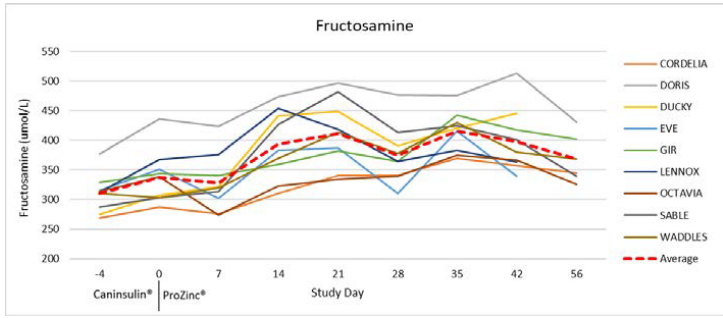

Fig 2. Fructosamine. Serum fructosamine was measured for each study subject. Fructosamine levels remained stable from Day 0 to Day 7 but started to increase at Day 14, suggesting dogs were not well regulated in the initial two weeks of ProZinc® therapy. This was expected during the time when appropriate doses were being determined. Nearing study conclusion, a downward trend in fructosamine demonstrates the animals were becoming controlled at the dose levels administered.

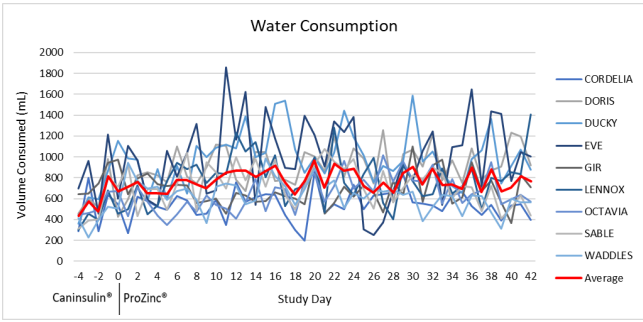

Fig 3. Water Consumption

Daily water consumption was measured for each study subject. Initially, water consumption increased following initiation of ProZinc® therapy, consistent with a lack of control while establishing appropriate ProZinc® doses. This upward trend reversed towards the end of the study when dogs were reaching ProZinc® doses closer to optimal.

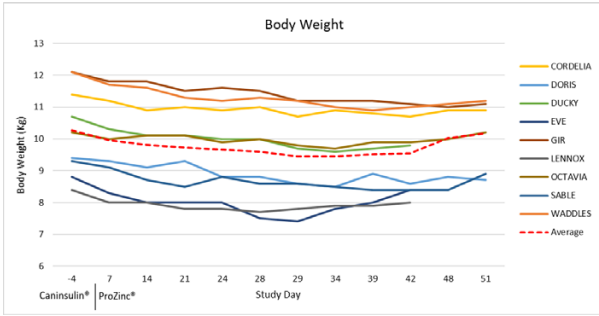

Fig 4. Body Weight

Body weight was measured for each study subject. As expected, body weight was slightly decreased following initiation of ProZinc® dosing; however, it began to increase as animal's insulin doses were titrated up and approached the ideal dose for each dog.

Conclusions:

1. ProZinc® Insulin controlled glycemic parameters and clinical signs in diabetic dogs when given once daily
2. ProZinc® Insulin showed a dose-dependent biphasic glucose lowering activity when given once daily
3. Clinical and glycemic control in diabetic dogs given Caninsulin® twice daily was similar to that seen with ProZinc® once daily.