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WHICH INSULIN AND WHICH DOSING REGIMEN IN 2006?

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During the past four years, new insulin products have been introduced to the USA, and more insulin products have gained FDA approval and will soon be commercially available. As these new insulins gain popularity, production of old and familiar insulins is being discontinued. Many questions have arisen regarding new insulin products. Concerns regarding protocols for changing insulin treatment of diabetic dogs or cats from one insulin product to another have also been voiced.

Most commercially available insulins are human analogue insulins, produced by recombinant DNA techniques. The structure of insulin is well preserved in different species, and usually consists of two polypeptide chains. The A chain (21 amino acids) and B chain (30 amino acids) are connected to one another or folded over by 3 disulfide bonds (Figure 1).

Human insulin differs from canine insulin by one amino acid. Amino acid number 30 in the B chain (B 30), which is threonine in humans, is replaced with alanine in dogs. Cat insulin differs from human insulin by four amino acids, and differs from canine insulin by three amino acids:

Position	Human	Dog	Cat
A 8	Threonine	Threonine	Alanine
A 10	Isoleucine	Isoleucine	Valine
A 18	Asparagine	Asparagine	Histidine
B 30	Threonine	Alanine	Alanine

SHORT ACTING INSULINS

There are three commercially available short acting insulins: regular insulin (humulin R® Eli Lilly, Novolin R® Novo Nordisk), lispro insulin (Humalog® Eli Lilly), and aspart insulin (Novolog® Novo Nordisk). Lispro insulin is a human analogue insulin in which proline at position B 28 and lysine at position B 29 were substituted with one another. In aspart insulin, another rapidly acting human insulin analogue, proline at position B 28 is substituted with aspartic acid.

Position	Human insulin	Lispro insulin	Aspart insulin
B 28	Proline	Lysine	Aspartic acid
B 29	Lysine	Proline	Lysine

When given SC to humans, lispro's onset of action is faster (5-15 minutes), and its duration of action is shorter (4-6 hours), compared to regular insulin (in which onset is 30-60 minutes and duration is 8-10 hours).[1,2] Onset and duration of action of SC aspart insulin in humans, are similar to values reported for lispro insulin and are also more rapid than regular insulin. The relatively slower and longer affect of regular insulin, as compared to lispro or aspart insulins is believed to be due to the fact that zinc present in the regular insulin solution promotes formation of large insulin hexamers that are slow to diffuse from the subcutaneous tissue into the circulation. The structural changes in the C-terminal of the B-chain in lispro and aspart reduce the formation of insulin dimers and hexamers and allow for more rapid absorption of insulin monomers from the subcutaneous tissue into circulation.

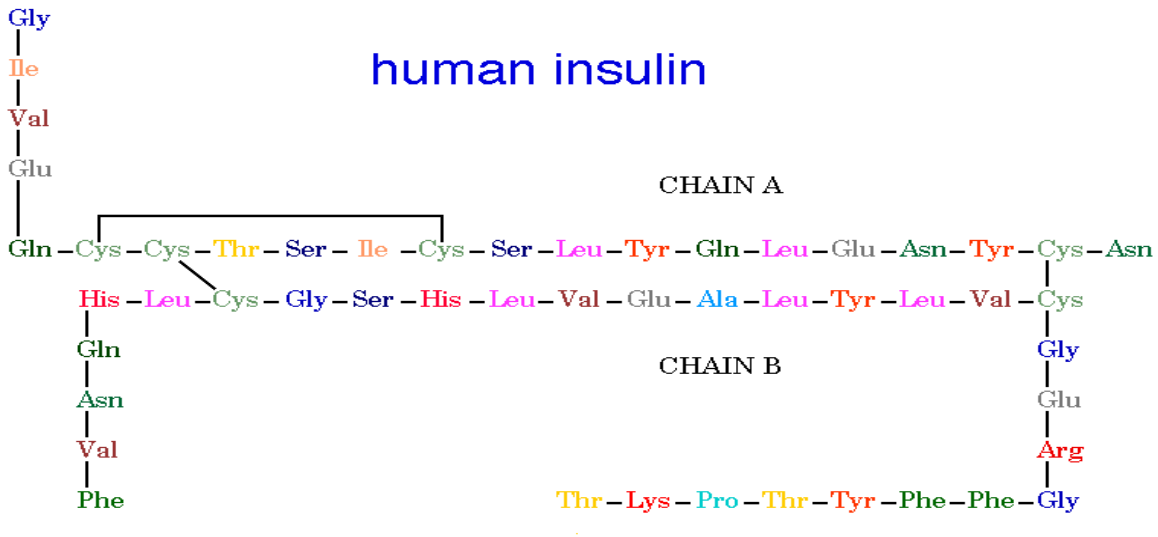

Figure 1.

In humans with diabetes mellitus, rapidly acting human insulin analogues are administered subcutaneously just prior to meals in order to reduce postprandial hyperglycemia. These rapidly acting human insulin analogues are administered subcutaneously, just prior to meals, in addition to a longer acting insulin which is given once or twice a day. While lispro insulin has been given safely to humans as an intravenous (IV) injection, most reports of lispro or aspart insulin describe subcutaneous administration of these drugs. Intravenous administration of lispro or aspart insulin has not been reported in clinical trials of humans with diabetic ketoacidosis (DKA). However, a small number of clinical trials has documented successful treatment of DKA in humans with subcutaneous (SC) administration of lispro or aspart insulin.[3, 4]

Regular insulin may be administered IV, intramuscularly (IM), or SC in dogs and cats. In veterinary medicine, regular insulin is used mainly for treatment of DKA and is administered IV as a continuous rate infusion or as an IM injection. While safe IV administration of lispro and aspart insulin to dogs has been documented, clinical trials of these insulins in dogs or cats with naturally occurring diabetes mellitus have yet to be reported.

Glulisine (Apidra® Aventis) is another rapidly acting insulin analogue which has been approved for use by the FDA but is not yet commercially available. Glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and lysine in position B29 is replaced by glutamic acid. The pharmacokinetics of glulisine insulin administered subcutaneously to humans are similar to those of lispro and aspart insulin.

INTERMEDIATE ACTNG INSULINS

Neutral Protamine Hagedorn

NPH (neutral protamine Hagedorn, isophane insulin suspension, Humulin N® Eli Lilly, Novolin N® Novo Nordisk) is presently produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli.* It is identical to human insulin. In the past, NPH insulin was also extracted from beef or pork. The insulin is combined with the fish protein protamine and zinc to prolong its duration of action. NPH insulin is administered to dogs and cats SC, every 12 hours at an initial dose of 0.5 U/kg. The dose is then adjusted based on clinical sings and blood glucose monitoring.

Porcine Insulin Zinc

Purified porcine insulin zinc (Vetsulin®, Caninsulin®, Intervet) is the only FDA approved insulin for dogs and cats. Porcine insulin is identical to canine insulin and differs from feline insulin by three amino acids. Its safe and successful use has been described in 53 diabetic dogs which were closely monitored for 60 days.[5] The recommended initial dose is 0.5 U/kg every 12 hours. As with any insulin, the dose is adjusted based on clinical signs and blood glucose monitoring. Pharmacokinetics and pharmacodynamics of purified porcine insulin zinc have also been reported in 25 diabetic cats before and after glycemic control was achieved. Peak plasma insulin concentration was recorded 1.7+/-0.1 hours after injection of the insulin, and a nadir of blood glucose was noted after 4.1+/-0.3 hours. Insulin and glucose concentrations returned to baseline within 12 hours of insulin administration, indicating that the insulin should be administered twice a day. There were no significant changes in pharmacokinetics and pharmacodynamics of the insulin when comparing in the first week of treatment to treatment 5 or 9 weeks later.[6]

Protamine Zinc Insulin

PZI (protamine zinc insulin, PZI VET®, IDEXX) has been previously thought of as a long acting insulin in cats. However, a clinical trial of 67 diabetic cats suggested that twice daily SC treatment with approximately 0.4 U/kg is needed for adequate clinical control.[7] PZI is composed of a mixture of 90% beef and 10% pork insulin. Similarly to NPH it contains the fish protein protamine and zinc, which facilitate delayed absorption and prolong duration of action.

Lente Insulin

Production of human lente insulin by recombinant DNA technology (insulin zinc suspension, Humulin L® Eli Lilly) was discontinued in early July 2005, due to decreased use of this insulin among human diabetics. Diabetic dogs and cats should begin treatment with one of the other insulins. There are no established guidelines for converting an established lente insulin dose to a dose of one of the other insulins available for treatment of diabetics. Decisions for establishing such an insulin dose should be made on a case by case basis, and should be monitored carefully by assessing clinical signs and glycemic control.

LONG ACTING INSULINS

Glargine Insulin

Glargine insulin (Lantus®, Aventis) was introduced to the USA in 2001. It is marketed as a long acting peakless insulin for use in human beings. Glargine insulin differs from human insulin in that asparagine at position A 21 is replaced with glycine and two arginine residues are added to the C-terminal of the B chain at position B 30.[1] Glargine is a human analogue insulin produced by recombinant DNA techniques. As with other human analogue insulins, the name is derived from the names of the amino acids that are used to alter human insulin. These substitutions result in a shift of the molecule's pH. Glargine insulin is injected in a clear solution with a pH of 4.0, and forms a microprecipitate at the physiologic, neutral pH of the SC space. These aggregates result in delayed, prolonged, and relatively constant absorption of insulin from the SC injection site. Because glargine is acidic, it can not be mixed with neutral insulin such as regular insulin.

In humans, glargine insulin is used as a once daily, long acting, peakless insulin that mimics the flat inter-prandial insulin secretion in non-diabetics. In diabetic

humans the onset of action of glargine insulin occurs 2-4 hours after SC injection, and the duration of action is 20-24 hours. Glargine insulin is supplemented with a rapid and short acting insulin (such as lispro or aspart) at meal times.[8]

Reports of the use of glargine insulin in veterinary medicine are limited to abstracts describing the use of glargine insulin in a small number of normal and diabetic cats. A dose of 0.5 U/kg administered SC every 12-24 hours appears to be safe and effective. Glargine insulin should be administered every 24 hours initially, and response to treatment should be assessed by evaluating serial blood glucose concentrations within 1-2 weeks. The dose and frequency of administration can then be adjusted based on clinical signs and glycemic control. Further studies are needed in order to better characterize the use of glargine insulin in diabetic dogs and cats.

Detemir Insulin

Detemir insulin (Levemir®, Novo Nordisk) is another long acting human insulin analogue which was approved for use by the FDA in June 2005 and may become commercially available in the future.[1]

Extended Insulin Zinc Suspension

Production of extended insulin zinc suspension (ultralente insulin, Humulin U® Eli Lilly) was discontinued in early July 2005, due to decreased use of this insulin among human diabetics and the increased use of other long acting insulins such as glargine. Diabetic dogs and cats that are well regulated with once daily treatment of ultralente insulin should be switched to once daily treatment with glargine insulin. Diabetic dogs and cats that require twice daily treatment with ultralente can be switched to any of the available insulin products. As with lente insulin, there are no established guidelines for converting an established ultralente insulin dose to a dose of one of the other insulins available for treatment of diabetics. Decisions for establishing such an insulin dose should be made on a case by case basis, and should be monitored carefully by assessing clinical signs and glycemic control.

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