Update on Insulin Therapy:  
What’s Available and When to Use It

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Overview and Classification of Insulin

Insulin is classified by source, duration of action, and preparation. Today, the majority of available insulin preparations are human recombinant or synthetic insulin. In fact, Vetsulin® is the only remaining animal source (porcine) insulin in use today. When classified by onset and duration of action, insulin preparations are classified as rapid-acting, short-acting, intermediate-acting, or long-acting. The rapid-acting and majority of the long-acting insulin preparations are human insulin analogs, which are created by modifying the amino acid structure of recombinant human insulin. In general, these alterations make absorption and duration of action more consistent and predictable. This has led to an overall decrease in the occurrence of hypoglycemic episodes in human diabetics. This is in comparison to crystalline insulin preparations (e.g. NPH, Vetsulin®, PZI) where the addition of protamine and/or zinc promotes the formation of insulin hexamers leading to a slower onset and longer duration of action. Hexamer dissociation is associated with greater variability in absorption and duration of action, and it increases the risk of hypoglycemic events.

Currently Available Insulin Preparations

Rapid-acting:  
- Insulin lispro (Humalog®)
- Insulin aspart (NovoLog®)
- Insulin glulisine (Apidra®)

Short-acting:  
- Regular insulin (Humulin® R, Novolin® R)

Intermediate-acting:  
- NPH (Humulin® N, Novolin® N)
- Lente insulin- 30% semilente + 70% ultralente (Vetsulin®)

Long-acting:  
- Insulin glargine- 100 U/ml (Lantus®, Basaglar®)
- Insulin glargine- 300 U/ml (Toujeo®)
- Insulin detemir- 100 U/ml (Levemir®)
- Protamine Zinc Insulin (ProZinc®)
**Insulin Therapy in Dogs**

Intermediate-acting insulin formulations continue to be the most commonly used and recommended insulin preparations for the management of canine diabetics. The two currently available intermediate-acting insulin formulations are NPH and Vetsulin®. The starting dose is 0.25-0.5 U/kg every 12 hours with acceptable glycemic control being achieved in most dogs with a dose of 0.5-1 U/kg every 12 hours. The long-acting insulin formulations have been evaluated in dogs, and there does not appear to be a clear benefit to using insulin glargine (Lantus®) or PZI (ProZinc®) in the management of dogs. Insulin detemir (Levemir®) results in improved glycemic control in some dogs but the potency (Levemir® starting dose: 0.1-0.2 U/kg) of the formulation limits its use in small dogs. The low potency of Lantus® and Toujeo® make these formulations useful in small dogs that are unregulated but have recurrent hypoglycemia with small doses (1-3 U) of NPH or Vetsulin®. Long-acting insulin analogs are an option for dogs in which acceptable glycemic control cannot be achieved with NPH or Vetsulin®.

The use of a rapid-acting insulin analog administered concurrently with NPH has been investigated in a small group of dogs. This protocol (i.e., administration of a rapid-acting insulin with an intermediate-acting maintenance insulin) is similar to protocols commonly used to manage human diabetics. In the trial, insulin lispro was administered with NPH at mealtime in six dogs that were considered to have well-regulated diabetes while receiving NPH but continued to have a profound postprandial spike in blood glucose. Subcutaneous insulin lispro at a dose of 0.1 U/kg was well tolerated and blunted the postprandial spike (decreased the blood glucose at 60 and 90 minutes). Although this approach may prove beneficial in dogs that have unacceptable glycemic control related to postprandial hyperglycemia, this combination protocol is likely not necessary for the majority of canine diabetics and increases the risk of hypoglycemia. When initiating this protocol, it is recommended that the maintenance insulin dose be reduced by at least as many units as the number of units of rapid-acting insulin being added (i.e., total units of insulin being administered is the same or less). This will hopefully decrease the potential for hypoglycemic complications.

**Insulin Therapy in Cats**

It is possible to achieve ideal glycemic control in most cats with twice daily administration of long-acting insulin formulations. The time-action profile of these insulins is more appropriate in cats than intermediate-acting insulins and higher remission rates are reported in cats receiving long-acting insulin preparations. Currently available formulations that are routinely used in cats include insulin glargine (Lantus®), PZI (ProZinc®), and insulin detemir (Levemir®). The recommended starting dose for these long acting formulations is 1-2 U/cat every 12 hours. The majority of cats will have acceptable glycemic control at a dose of 1-6 U/cat every 12 hours. Twice daily insulin administration is recommended and is more likely to result in good glycemic control. If it is not possible to administer insulin twice daily, once daily administration of Levemir® or Toujeo® (starting dose: 1-2 U/cat) may provide acceptable control of clinical signs and decrease the occurrence of complications associated with untreated diabetes mellitus.
Toujeo® has been studied in healthy cats, but there is limited information about clinical use available.

**Insulin Therapy for Diabetic Ketoacidosis (DKA)**

The three protocols for the treatment of DKA that have been described in veterinary medicine include administration of human regular insulin via intravenous constant rate infusion (CRI), hourly intramuscular (IM) insulin, and IM insulin administered every 4 to 6 hours. Many clinicians consider intravenous CRI the standard of care although the ideal route of administration remains a matter of debate. More recently, insulin lispro and insulin aspart administered as an intravenous CRI have been successfully used to treat DKA in dogs. It was concluded that these rapid-acting analogs are a safe and effective alternative to regular insulin although a clinically significant benefit was not identified.

To the author’s knowledge, subcutaneous administration of rapid-acting insulin analogs for the treatment of DKA in dogs and cats has not yet been investigated. This treatment may provide an alternative to CRI and IM regular insulin protocols in cats and dogs and may have advantages when compared to traditional protocols. Results obtained in the author’s research laboratory in healthy cats combined with the clinical data obtained in people suggests that a subcutaneous insulin aspart protocol could be an effective treatment for cats with DKA. This type of intermittent treatment protocol could be a better option for intermediate care wards or veterinary facilities that do not have an intensive care unit or access to numerous intravenous fluid pumps. The ability to use rapid-acting analogs to treat dogs and cats with DKA may be of greater importance in the future if regular insulin becomes unavailable due to decreasing demand for the management of human diabetics.

**References**
