INSULIN PRODUCTS

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The number and types of insulin preparations available in the United States is constantly changing, thus students should refer to recent drug resources for a current list of products. In general, insulin products can be grouped into four categories: regular, the protamine products, the lentes, and the modified insulins (Insulin lispro or insulin aspart). Each of these insulin products or derivatives differs from the others in physical and chemical properties and use profile as described below.

Physical-chemical characteristics of insulin preparations

<table>
<thead>
<tr>
<th>Type</th>
<th>Zn Content (mg/100 units)</th>
<th>pH</th>
<th>Buffer</th>
<th>Modifying Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular Insulin</td>
<td>0.01-0.04</td>
<td>2.5-3.5 (acidified)</td>
<td>7.0-7.8 (neutral)</td>
<td>-----</td>
</tr>
<tr>
<td>NPH Insulin</td>
<td>0.01-0.04</td>
<td>7.1-7.4</td>
<td>Phosphate</td>
<td>0.3-0.6 mg Protamine</td>
</tr>
<tr>
<td>PZI</td>
<td>0.15-0.25</td>
<td>7.1-7.4</td>
<td>Phosphate</td>
<td>1.0-1.5 mg Protamine</td>
</tr>
<tr>
<td>SemiLente Insulin</td>
<td>0.2-0.5</td>
<td>7.2-7.5</td>
<td>Acetate</td>
<td>None</td>
</tr>
<tr>
<td>Lente Insulin</td>
<td>0.12-0.25</td>
<td>7.2-7.5</td>
<td>Acetate</td>
<td>None</td>
</tr>
<tr>
<td>UltraLente Insulin</td>
<td>0.12-0.25</td>
<td>7.2-7.5</td>
<td>Acetate</td>
<td>None</td>
</tr>
</tbody>
</table>

Regular Insulin

Amorphous insulin was the first form made available for clinical use. Further purification afforded crystalline insulin that is now commonly called regular insulin. Insulin injection USP is a solution made from crystalline zinc insulin. It is the only insulin that is a solution, all others are suspensions. For some time, regular insulin solutions have been prepared at a pH of 2.8 to 3.5; if the pH were increased above the acidic range, particles would be formed. However, more highly purified insulin can be maintained in solution over a wider range of pH even when unbuffered. Neutral insulin solutions have greater stability than acidic solutions; neutral insulin solutions maintain nearly full potency when stored up to 18 months (refrigerated).

Regular insulin has a rapid onset (30 minutes after SC administration) and a short duration of action (5-12 hours). Maximal effects are seen in 1-3 hours and duration and intensity of action increases with dosage. The plasma half-life following SC administration is roughly 1.5 hours. After IV administration, the onset of regular insulin is within 15 minutes and the duration is decreased to 30—60 minutes. Maximal effects occur within 15—30 minutes after IV injection with a plasma half-life of approximately 9 minutes.

This onset and duration profile generally precludes the use of regular insulin in the daily treatment of diabetes because of the number of injections required. It is used instead for treating medical emergencies, such as ketoacidosis, diabetic coma, and surgical complications. Due to the increasing interest in achieving fine control over the blood glucose level, regular insulin may be incorporated into multiple daily injection protocols in combination with a modified insulin product. Regular insulin can be mixed with
modified insulin preparations if one is directed to do so. Buffered insulin preparations are also available for use in the insulin pumps required for continuous subcutaneous infusion of insulin (CSII) - another method to achieve fine blood glucose control.

Protamine Insulins

Many attempts have been made to prolong the duration of action of insulin; for example, the development of insulin forms possessing less water solubility than the highly soluble (in body fluids) regular insulin. The insulin products containing protamine were originally developed in 1936 as a result of these efforts. In the first product, insulin was combined with zinc and an excess of protamine, a basic protein obtained from the testes of fish, in a buffered solution to form a protamine-zinc-insulin (PZI) complex. The complex has an isoelectric point close to physiologic pH; hence, it is less soluble in extracellular fluids than is insulin. As a result of decreased solubility, protamine insulin preparations are less readily absorbed from body tissue. This accounts for the longer onset (approximately 4-8 hours) and the prolonged duration of action (longer than 36 hours). The peak effects occur 14—24 hours following SC administration. PZI should not be used to treat diabetic coma or in emergency situations. PZI is administered via intermittent SC injections only. Because of concerns about too little effect in the daytime and too much at night, PZI lacked popularity, and was discontinued in the United States in 1991.

A related product, Neutral Protamine Hagedorn insulin (NPH, also called isophane), however, developed at Nordisk Insulinlaboratorium in Denmark in 1946, achieved wide acceptance and these products continue to be widely used. The term isophane is derived from the Greek iso and phane, meaning equal and appearance, respectively. Like PZI, NPH insulin is a complex of insulin, zinc, and protamine, but it is prepared by the careful control of the protamine/insulin ratio and the formation of a crystalline entity containing stoichiometric amounts of insulin and protamine. This NPH insulin contains less protamine than does PZI. It has a particle size of 30 um.

NPH insulin is administered via the SC route by intermittent injections only. NPH insulin has a quicker onset of action (roughly 1-1.5 hours following SC administration) than PZI, but a shorter duration of action (24 to 28 hours). NPH insulin effects peak at 4—12 hours after administration. Because of the more rapid onset of action, it is usually not necessary to supplement NPH insulin with regular insulin, as was often the case with PZI. The 24-hour duration of NPH insulin is more compatible with day-to-day living than the 36-hour duration of PZI. This agent should not be used for diabetic coma or in emergency situations.

A number of premixed insulins having a fixed ratio of NPH insulin to regular insulin are also available. Preparations available in the United States consist of 70% NPH and 30% regular insulin (70/30) and 50% NPH and 50% regular insulin (50/50). Other premixed preparations of 90/10 and 80/20 are available in Europe.
**Lente Insulins**

Concerns over the potential antigenicity of protamine (obtained from fish) in PZI and NPH insulins led to the development of Lente insulins in 1951; thus these preparations are unique in that they do not contain a protein modifier to prolong their action. Lente insulins are prepared by precipitating insulin from an acetate buffer (instead of phosphate), by the addition of zinc. At relatively low zinc concentrations, an amorphous powder (semilente insulin) precipitates, and at higher zinc concentrations, a microcrystalline material (ultratente insulin) precipitates.

Ultralente insulin (extended insulin zinc suspension) has a particle size of 10 to 40 μm and is relatively insoluble, has a slower onset (4 hours), and longer duration of action (36 hrs, comparable with PZI). Its peak activity usually occurs at 10-30 hours after SC administration. Ultralente insulin should not be used in the case of diabetic coma or emergency situations. Ultralente insulin is administered via intermittent SC injections only.

Semilente insulin (prompt insulin zinc suspension) has a smaller particle size (2 μm) and is more soluble and has a quicker onset (from 1 to 1.5 hours following SC administration, with peak effects occurring anywhere from 5—10 hours) and a shorter duration of action (10-16 hrs, comparable with that of regular insulins). Semilente insulin is not commonly used but it can be administered alone when rapid action is desired, except in the case of diabetic coma or emergency situations, for which regular insulin is the drug of choice. Semilente insulin is administered SC and should not be administered by the IV route.

A third type of insulin suspension, Lente insulin, is a 70:30 mixture of Ultralente and Semilente insulins. Lente insulin has a rapid onset (2-4 hrs) and an intermediate duration of action (about 24 hrs, comparable with that of NPH insulin) following SC administration. The peak activity of lente insulin occurs 7—15 hours. Because of its rapid onset and intermediate duration, lente insulin is well suited for once-a-day administration and has been well accepted for use in this manner. This agent should not be used in the case of diabetic coma or emergency situations. Lente insulin is administered via intermittent SC injections only.

Lente insulins are chemically incompatible with the PZI and NPH insulins because of the different buffer system used in the preparation of these insulins; an acetate buffer is used in Lente insulins and a phosphate buffer is used in PZI and NPH insulins. Thus the lente insulins should not be mixed with insulin preparations containing phosphate buffers, because phosphates alter the solubility characteristics of the lente crystals and influence the onset and duration of action.

**Insulin Lispro and Analogues**

Strict glycemic control often is difficult to achieve, primarily because conventional subcutaneous insulin formulations do not mimic normal physiology in which the pancreas quickly releases insulin in response to an increased glucose load, such as that
observed after a meal. For example, even though regular insulin is considered to be fast acting, it must be given between 30 and 60 minutes before meals to achieve optimal postprandial glycemic control. This slow onset is a result of the strong propensity for self-association observed for that conventional insulin products, leading to the formation of dimers and subsequently to hexamers which dissociate only slowly to absorbable monomers.

Thus considerable effort has been extended over the past decade to develop insulin derivatives that would dissociate more rapidly and therefore be more quickly absorbed from the site of subcutaneous administration. The first product of these research to be approved by the FDA is lispro insulin, a synthetic insulin analog prepared by recombinant DNA methods in which the amino acids at position B28 (proline) and B29 (lys) in the beta chain of human insulin have been inverted. This structural modification results in enhanced dissociation into dimers, then monomers in concentrated solutions, and more rapid absorption, higher peak concentrations and a shorter duration of action. Insulin lispro binding to insulin receptor and immunogenicity are unaffected by the structural change. Lispro insulin can decrease postprandial hyperglycemia, and may be more convenient for some patients because it can be injected immediately before meals. Whether it decreases hypoglycemia or glycosylated hemoglobin levels remains to be established.

Lispro is supplied in a solution containing 100 IU/ml in 10 mL vials, or 1.5 mL cartridges for pen injectors (Becton Dickinson’s or Novo Norids’). It may be given in the same syringe with long-acting insulins, but its absorption may be delayed and prolonged by mixing with the protamine in NPH insulin. Lispro insulin injected 0-15 minutes before a meal results in peak serum insulin concentrations in 30-90 minutes. In one study, peak concentrations of serum insulin was 2.9 times greater and the time to peak was 4.2 times earlier for the insulin lispro versus regular human insulin patients. The duration of action for lispro insulin is only 3-4 hours. These differences in action allow for more flexibility in dosing with lispro insulin and may improve glycemic control in some patients while decreasing the risk of hypoglycemia with multiple injection therapy. Insulin lispro is not recommended for IV administration. Insulin lispro is a buffered insulin and is commonly used for insulin therapy in patients who wear external SC insulin infusion pumps.

**Insulin Delivery**

Progress in alternative routes of delivery of insulin have been prompted by problems associated with conventional insulin therapy. First, various types of electromechanical devices (infusion pumps) have been developed with the aim of reducing fluctuations in blood glucose levels associated with conventional insulin therapy (subcutaneous injections). These continuous-infusion pumps are either close-loop or open-loop systems. The ultimate goal of research in this area is to develop a reliable implantable (miniature) device, for long-term use, that would eliminate the need for daily administration and monitoring of blood glucose levels. The second area of research is to study alternative routes of administration such as oral, nasal, and rectal. Preliminary results indicate that the absorption of insulin at these sites is not uniform and is unpredictable. The third
approach to correcting the problems of conventional insulin therapy is to supplement the defective pancreas by transplantation with a normally functioning pancreas from an appropriate donor. The major problem with this approach is the rejection of the donor pancreas by the recipient and problems associated with the draining of exocrine enzymes. A modified procedure is to transplant only viable pancreatic islet cells or transplanting fetal or neonatal pancreas. The possibility remains, however, that in type I diabetes, the newly transplanted pancreatic beta-cells could be destroyed by the same autoimmune process that caused the disease in the first place.