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Evolution of Insulin: From Human to Analog

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ABSTRACT

The development of insulin analogs has made improved treatment of type 2 diabetes possible. In this article, structural alterations, pharmacokinetics and pharmacodynamics, clinical end points, and safety issues are reviewed for the currently available basal insulins, rapid-acting insulins, and premixes. The flatter activity profiles of insulin glargine and insulin detemir translate into good clinical efficacy with a lower risk of hypoglycemia relative to neutral protamine Hagedorn insulin. Weight gain is consistently lower with insulin detemir than with neutral protamine Hagedorn insulin. Insulin degludec, licensed in Europe and Japan but not yet in the United States, has a mean half-life of 25.4 hours, a duration of action of >42 hours, and low variability. In trials in type 2 diabetes, rates of nocturnal hypoglycemia were lower with insulin degludec than with insulin glargine, and more flexible; once-daily dose timing was shown to be possible. Insulin lispro, insulin aspart, and insulin glulisine are rapidly absorbed after injection and thus provide better coverage of the post-prandial glucose surge compared with human insulin. Trials and meta-analyses show that reductions in glycated hemoglobin are similar and control of postprandial glucose is better with the rapid-acting analogs versus human insulin. Convenience is greater for patients because the analogs can be injected just before a meal. In premix or biphasic insulins, a proportion of the rapid-acting analog is protaminated, providing both rapid-acting and intermediate-acting components in one formulation, thus reducing the number of injections required. Alterations to human insulin have resulted in improvements in safety, efficacy, tolerability, and convenience for patients.

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The history of insulin therapy has been one of continually evolving improvement. Since insulin was first isolated in 1921, milestones in this evolution have included the development of a slower-acting preparation in the late 1940s, neutral protamine Hagedorn insulin, and the use of recombinant technology to enable production large amounts of insulin in 1977 (**Figure 1**). This synthetic insulin was named "human insulin" to distinguish it from the earlier preparations derived from animal sources. Further milestones were the introduction of rapid-acting insulin analogs in the 1990s and long-acting basal analogs in the early 2000s.

The ever-increasing prevalence of type 2 diabetes and longer life expectancy of patients with diabetes mean that the use of and demand for insulin therapy will continue to grow. This article reviews recent developments in insulin that have improved the treatment of type 2 diabetes. We will focus first on the basal or long-acting insulin analogs, because these are the most widely prescribed insulins in type 2 diabetes. We will then briefly consider the rapid-acting analogs, used primarily in advanced type 2 diabetes, and premix insulins, which may be used to initiate or optimize insulin therapy.

BASAL INSULINS

Where Are We Currently?

Currently, widely used basal insulins are the intermediate-acting neutral protamine Hagedorn insulin and the basal analogs insulin glargine (Lantus; Sanofi, Paris, France) and

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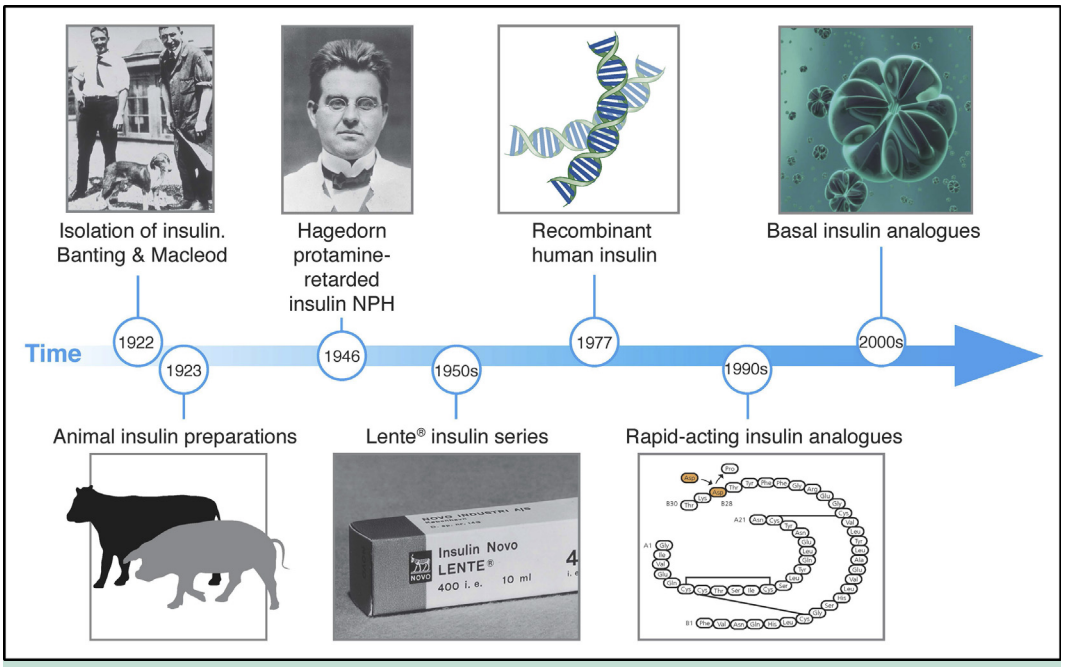

Figure 1 Milestones in the evolution of insulin therapy. NPH = neutral protamine Hagedorn.

insulin detemir (Levemir; Novo Nordisk Inc, Plainsboro, NJ). One additional analog, insulin degludec (Tresiba; Novo Nordisk Inc), has been licensed for use in Europe and elsewhere, but approval in the United States will be contingent on the results of a dedicated cardiovascular outcomes trial that is currently in progress.

Use of the basal analogs has enabled patients with type 2 diabetes to achieve equivalent levels of glycemic control, with a lower associated risk of hypoglycemia, compared with neutral protamine Hagedorn insulin.[1-4] However, only a proportion of patients achieve levels of glycemic control that meet current guidelines, suggesting there is still room for improvement. Indeed, although the aim is for exogenous basal insulin to match the body's own physiologic basal insulin output as closely as possible, subcutaneous injection substantially changes the kinetics of insulin exposure. Endogenous insulin is secreted by the pancreas directly into the portal vein, from where it is transported to the liver. On the other hand, subcutaneously administered insulin is absorbed into the systemic circulation, so for sufficient insulin to reach the liver and suppress endogenous glucose output, peripheral tissues are inevitably overexposed. This overexposure has been suggested as one of the possible causes of insulin-associated weight gain, a concern that deters many patients from initiating insulin therapy.[5]

Furthermore, the pharmacokinetic profile of injected insulin differs from that of endogenous insulin secretion, in which a steady rate of basal output is augmented by rapidly produced peaks in response to meals. Absorption of an insulin injection tends to follow a profile that increases to a peak before "tailing-off." In the case of basal insulins, this profile is protracted, but it may be only a poor approximation of the smooth flat profile of basal endogenous insulin secretion seen in the healthy state. This discrepancy increases the risk of hypoglycemia when insulin levels are too high relative to food intake or hyperglycemia when levels are low.[6] The profile of absorption also can vary between patients and even from injection to injection in the same patient. Therefore, the blood glucose–lowering effect may vary not only across the day but also day to day,[7] making it difficult to calculate correct dosing. Finally, with once-daily dosing, subcutaneously injected basal insulin can become depleted in <24 hours, increasing the risk of hyperglycemia during the periods with no or insufficient insulin present.[6]

Method of Protraction of Basal Insulin Analogs

Different approaches have been taken to modify the kinetics of basal insulins to retard absorption from the injection depot. Protraction initially was achieved through varying the components of the insulin mixture in the pharmaceutical formulation. For example, neutral protamine Hagedorn insulin consists of a complex of insulin and zinc with protamine, a fish protein that reduces its solubility.[8] This gave rise to an intermediate-acting insulin with a duration of action of 12 to 18 hours, with glucose-lowering effect peaking at approximately 4 hours.[9] A disadvantage of neutral protamine Hagedorn insulin is its need for resuspension before injection, which is a major source of variability in the actual dose given.[9]

The next step was to modify the structure of the insulin molecule itself, by replacing or removing amino acid residues in the A or B chains, and in some cases adding side chains (**Figure 2**). Insulin glargine was modified by the