Advances in insulin therapy
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Abstract
The grand dame of diabetes pharmacotherapy, nearly a century old, insulin continues to be the subject of discovery and innovation. Fresh research, combined with extensive clinical experience, has brought newer facets of insulin use to the fore. Thus, insulin still exudes maiden charm.

This review covers recent advances in the clinical pharmacology of insulin.

Keywords: Diabetes pharmacotherapy, Insulin.

Insulin Types
Insulin can be classified based upon the chemical structure and duration of action. Human insulin is now manufactured by recombinant DNA technology, using either E coli or Saccharomyces vectors. Insulin analogues are also available in which certain aminoacid substitutions or other modifications are done to achieve a particular pharmacokinetic profile. Insulin made by different manufacturers cannot be substituted for each other. Regular human insulin is classified as short acting insulin, while the analogues aspart, lispro and glulisine insulin are correctly termed as rapid acting. Regular insulin should ideally be administered 30 minutes prior to meals, though the rapid acting analogues may be injected immediately before or after food intake.

The only basal human insulin now available is NPH (neutral protamine Hagedorn). Combinations of regular insulin, aspart insulin or lispro insulin, in the same preparation with NPH insulin, in ratios of 25:75, 30:70, or 50:50, are available for use as well. These premixed insulins are the most commonly prescribed insulins, not only in Pakistan, but in China and India as well. Various proportions of short and intermediate acting insulin (25:75, 30:70, 50:50) can be used in clinical practice.

Novel Rapid Acting Insulin Analogues
Modern rapid acting insulins include lispro, aspart, and glulisine.

Lispro
Insulin lispro is a r-DNA insulin analogue which was formulated on the premise that insulin-like growth factor-1 (IGF-1) which is structurally similar to insulin, does not tend to self associate. In the B chain of natural human insulin, lysine lies in the B29 position and proline in the B28 position. Lispro is produced by inverting position of two amino acids. In lispro B chain, lysine lies in B28 position and proline lies in 29 position. The inversion of proline at position 28 with lysine at position 29 blocks formation of insulin dimer and hexamer and allows larger amount of active monomeric insulin to be available for post-prandial or after meal injections. Lispro has rapid onset of action in 15-30 min and peak action in 30-60 min and action lasts about 3-4 hours Lispro is approved for use in pregnancy and in children above three years of age.

Aspart
Insulin aspart is a biosynthetically modified analogue, in which a single proline amino acid at position 28 of the insulin B chain has been replaced with an aspartic acid residue. In all other respects, insulin aspart is homologous with and structurally identical to native human insulin. Its pharmacokinetic properties are similar to those of lispro.

Replacement of a proline amino acid residue by aspartic acid disrupts an important interaction between monomer peptide chains, allowing rapid dissociation of hexamers and dimers into monomers. In native insulin, dimers are stabilised by an interaction at the monomer-monomer interface between proline B28 and glycine B23. Replacement of proline B28 with aspartic acid removes this interaction. Repulsion between the charged aspartic acid and the nearby glutamic acid B21 may also contribute to the rapid dissociation of insulin aspart into monomers. The amino acid change in insulin aspart reduces the strength of binding between insulin molecules in solution by blocking a single interaction between insulin chains. Insulin aspart remains physically stable, resulting in low risk of pump occlusion due to crystalline aggregation or precipitation. It also remains chemically stable, retaining pharmacological potency when used in an infusion pump and so is suitable for use in continuous subcutaneous insulin infusion pump. Aspart is approved for use in pregnancy and in children above two years of age. Aspart is the only rapid acting
analogue which has successfully been combined with a long acting analogue.²

Glulisine
Glulisine is a human insulin analogue that is a rapid-acting, parenteral blood glucose lowering agent. Insulin glulisine is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli (K12). Insulin glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid.³

A category C drug, it is not approved in pregnancy and in children 4 years and below. Moreover it was found to be incompatible with Dextrose solution and Ringers solution and, therefore, cannot be used with these solution fluids.

Novel Basal Insulin Analogues
Basal insulin analogues available across the world are glargine, detemir, and the ultra-long acting degludec insulin.

Glargine
Glargine is an acidic long acting analogue which differs from human insulin in that in A21 of A chain, there is substitution of asparagine with glycine, and in position B30 of B chain there is addition of two arginine residues. When injected into skin at neutral pH, there it forms precipitates which delays its absorption and responsible for its longer duration of action. Its of, duration of action is upto 24 hours, it has a peakless profile, and causes less hypoglycaemia when compared with NPH.⁴ The major drawback of glargine is weight gain, and there is concern about increased risk of cancer. Glargine is approved for use in children above six years of age, but is not approved for use in pregnancy.

Detemir
The long-acting analogue detemir differs from human insulin in two ways: deletion of amino acid Threonine at position 30 of beta chain, and addition of 14 carbon aliphatic fatty acid to epsilon amino group of lysine in position B29. These changes enable detemir to bind with albumin reversibly and also facilitate formation of multimeric complexes within subcutaneous tissue which prolongs the duration of action.⁵ Detemir is weight neutral, any may help weight loss in obese subjects, is not associated with an enhanced cancer risk, and is characterized by less inter individual variability as compared to glargine. Detemir is approved for use in children above two years of age, and for use in pregnancy.

Degludec
Degludec is a novel ultra-long acting insulin analogue, currently available in Europe, Japan and Mexico. It differs from human insulin by the deletion of threonine of B30, and addition of 16 chain carbon fatty di-acid to lysine of B29 with a glutamic acid as a spacer. This formulation allows degludec to form multiple hexamers which dissociate slowly after subcutaneous injection and are responsible for its longer duration of action. In addition, binding to albumin also contributes to its longevity in circulation. It results in long, flat, extended insulin profile, released smoothly without any peaks and has no inter subject variability.⁶ Its unique advantage is its ultra long acting profile, which reduces the number of doses required for basal coverage, and allows flexibility in frequency of dosage. There is less occurrence of hypoglycaemia, and better control of postprandial blood glucose when compared to glargine.

Novel Premixed Insulin Analogues
Degludec plus is the only premixed insulin in which both rapid acting and long acting components are analogue compounds: aspart and degludec.⁷ Premixed aspart (BIAsp 30 and BIAsp 50) and premixed lispro (BILis 25 and BILis 50) are composed of rapid acting analogues combined with traditional NPH insulin. Premixed aspart is approved for use in children above10 years of age, and is classified as a category B drug for use in pregnancy. Premixed lispro is approved for use in persons above 12 years of age, and is a category B drug for pregnancy.

Insulin Delivery Devices
Apart from the traditional needles and syringes, various disposable and reusable pens are currently used to administer insulin. This seemingly statement hides the variety of syringes (40 IU/ml, 100IU/ml), needle length (4mm, 7mm), and needle gauge (29 to 31 g) that are available in the market. Physician should ensure that appropriate syringes and needles, or cartridges and pens and used together, to prevent errors in administration.

Choosing an Insulin Preparation/Device
The choice of insulin preparation, in Pakistan, as well as other pay-from-pocket markets, depends first and foremost upon economic factors. However, one should try to calculate the holistic cost of insulin therapy, rather than focusing on the direct expenses of medication alone. Using a safer, better tolerated, more convenient, insulin preparation (such as an analogue) or modern delivery device, which needs less monitoring or rigid storage facilities, and is associated with a lower "index of intrusion" in one’s daily lifestyle, may turn out to be more economical for an individual with diabetes.

Newer Insulin Regimes
Insulin regimes have conventionally been classified as
basal, premixed and basal-bolus. However, with an increase in the number of insulin preparation, and recent studies on novel insulin regimes, a re-classification is in order.

Choosing an Insulin Regime

Not all insulins are alike, and neither are all insulin regimes the same. Choosing the correct regime is important, as a wrong choice may impact adherence, and lead to hypoglycaemia or poor control. An insulin regime is chosen based upon a combination of evidence-based and experience- or environment-based factors. While a separate insulin may work for initiation, one may have to up-grade or intensify the regime if control is not achieved. Intensification of therapy has been defined as a change in insulin formulation, regimen, frequency or dosage, or addition of other therapeutic modalities, with a view to improving glycaemic control. Similarly, down-gradation or de-escalation of therapy (decrease in number of units &/or the number of doses) is indicated if glucotoxicity or co morbid illness resolves, or the patient is unwilling for intensive treatment.

30:70 mixtures are able to achieve successful therapeutic outcome because of the simplicity of use by both physician and patient. One can begin with a single — dose insulin analogue regime, which will achieve adequate HbA1c in 45% cases. In the rest, upgrading or intensifying to a two dose regime will achieve control in a total of 75% patients. A further intensification to three — dose regime will bring down HbA1c to target in a total of 87-90%, patients. Using the same insulin to initiate, titrate, intensify and control diabetes is beneficial because it becomes easier for all members of the health care team — the nurses, diabetes educators, chemists, physician assistants — not to mention the patients and doctors, to use.

Insulin Combinations

Insulin is being studied as a combination with glucagon-like peptide (GLP-1). This fixed concentration combination (FCC), (as opposed to fixed dose combination) provides basal insulin analogues(detemir or glargine) with GLP-1 analogues (liaglutide or lixisenatide) in a once daily subcutaneous injection, and resolves insulin as well as incretin deficiency.

Conclusion

Insulin has helped millions of people with diabetes live normal lives. Newer, modern insulins and insulin accessories have revolutionized the practice of diabetes care today. An understanding of modern insulins available, coupled with knowledge of current delivery devices and novel insulin regimes can help improve glycaemic control, while ensuring high standards of safety and tolerability.

References