Chapter

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Rapid Acting Analogues in Diabetes Mellitus Management

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INTRODUCTION

The WHO estimated the prevalence of diabetes to be 177 million individuals worldwide in the year 2000 and predicts that it will rise to at least 300 million individuals by 2025[1]. The discovery of insulin more than 80 years ago is considered as one of the greatest medical breakthroughs of the 20th century[2]. However, pancreatic insulin did not evolve for exogenous administration, and subcutaneous injection therapy has not succeeded in normalizing glycemic control despite the great efforts devoted to improvements in insulin preparations and injection regimens. Until the 1980s insulin was obtained by extraction and purification from pancreas of cows and pigs (bovine and porcine insulins). The use of recombinant DNA technology has enabled large-scale production of human insulin. Recently, rDNA and protein engineering techniques that alter the amino acid sequence of insulin have been used to produce 'monomeric analogues of insulin, which are more rapidly absorbed from the site of injection (e.g. insulin lispro or aspart)[3].

Conventional Insulin Limitations

Regular human (soluble) insulin is absorbed into the bloodstream slowly and with poor reproducibility when it is injected into subcutaneous tissue. This delay is due to the hexameric form of insulin at high concentration, which has to be degraded (by dilution) to monomers in the subcutaneous tissue before absorption. To overcome this slow absorption rate and to make it closer to physiological, regular human insulin was recommended to be injected 30-60 minutes before a meal. While this was practised there was risk of pre-prandial hypoglycemia if the meal is missed or delayed[4]. Furthermore, often it is observed that this recommendation is inconvenient and difficult to comply with. This leads to lack of compliance to timing of injection in relation to the meal and the consequent rise in postprandial blood glucose levels. Moreover, prandial hypoinsulinemia and postprandial hyperinsulinemia may occur because of the slow onset, but prolonged duration of action of regular insulin[4]. Thus, the pharmacokinetics of conventional insulin preparations failed to match the physiological insulin secretion profile, and due to this in most patients it was virtually impossible to obtain glycosylated hemoglobin (HbA1c) values around or < 7.0%[5-7].

Another drawback with conventional insulins is that a considerable number of patients have been characterized by a degree of control with a huge day-to-day variation in glycemic level[5,6]. This variation is a result of several factors including variability in insulin action and insulin absorption leading to both within- (intra-individual) and between- (inter-individual) variability.

The above limitations of conventional insulins led to producing insulin analogues that more closely mimic the physiological insulin secretion. Insulin analogues or "modern insulins" are characterized by action profiles that afford more flexible treatment regimens with a lower risk of the development of hypoglycemia.

Rapid Acting Analogues Addressing Unmet Needs

Rapid acting insulin analogues bear a close resemblance to the normal mealtime insulin and mimic the physiological profile as compared to an injection of regular human insulin, and therefore improve postprandial glycemic control. As these agents are short acting (and hence a shorter duration of action), they do not contribute much to between-meal insulin level. These rapid acting analogues can be given immediately

before the meals and is preferred by patients as well as health care professionals.

An insulin analogue is an insulin molecule whose composition is altered in order to yield certain advantages over standard human insulin, while retaining the same biological effect. Insulin lispro was the first to be synthesized followed by insulin aspart and then insulin glulisine.

The relatively slow absorption of regular insulin is attributed to the fact that when zinc ions are added to the solution of dimers that make up regular insulin, the molecules associate, and hexamers are formed. These larger molecules diffuse slowly into the circulation, whereas the insulin dimers and monomers are absorbed more quickly.

Monomeric insulin's are absorbed 2 or 3 times faster than standard soluble insulin. Since these act without delay they can be injected subcutaneous shortly before or just after meal. The amino acid changes that have been made to each formulation result in a more weakly associated hexamer, the rapid dissociation of which results in a corresponding rapid onset and peak as well as shorter duration of action, compared with standard soluble insulin. This should result in better post-prandial control and less hypoglycemia. Compared with standard soluble insulin, rapid acting insulin analogues may produce a modest but significant reduction in HbA1c when used in continuous subcutaneous insulin infusions, and are very much preferred by patients[17].

Rapid acting insulin analogues provide an improved glycemic control both pre-prandial as well as post-prandial in patients with diabetes mellitus[8]. Better glycemic controls, as assessed by measurement of serum glucose excursions over 4 and 6 hours was achieved with insulin aspart administered immediately or 30 minutes before a meal than with regular insulin administered immediately or 30 minutes before a meal in single dose studies in both type 1 and 2 diabetes[9-11]. Postprandial glycemic control was more effective with insulin aspart than with regular insulin in randomized, non-blind comparisons in patients with type 1 diabetes. Postprandial glucose levels were generally significantly lower in patients receiving insulin aspart than in regular insulin recipient in all trials[12-15].

As regards inter-individual variation, rapid acting analogues are devoid of inter-individual variations and the variability is significantly less than that observed with regular insulin[16].

Insulin lispro, the first rapidly acting analogue that was made available for clinical use, differs from regular insulin by virtue of its capacity to dissociate rapidly into monomers in subcutaneous tissue. It 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 probably because of differences between the C-terminal portion of the B chain of IGF-1 and that of insulin. Inversion of the lysine of B29 and the proline of B28 of human insulin confers a conformational change that results in a shift in the normal binding of the C-terminal portion of the B chain, which in turn reduces the formation of dimers and hexamers (Fig. 1).

The immunogenic profile of insulin lispro is similar to that of recombinant insulin[18]. Even before exposure to insulin lispro, there is an increase in cross-reactive antibodies (i.e., serum reacts with both insulin lispro and human insulin) but not in insulin-specific or lispro-specific antibody levels[18]. These antibodies decrease over time and have no clinical consequences[18,19].

Insulin aspart is a novel rapid-acting analogue developed by replacing proline at B28 with aspartic acid (Fig. 2).

Studies have shown that insulin aspart has twice as rapid onset of action and reaches a higher peak than soluble human insulin in a shorter span of time (Fig. 3). Therefore it provides better PPG control with low risk of hypoglycemia. The action of insulin aspart like other rapid-acting analogues lasts for only 3-5 hours unlike soluble human insulin whose action lasts up to 8 hours after injection into the subcutaneous tissue.

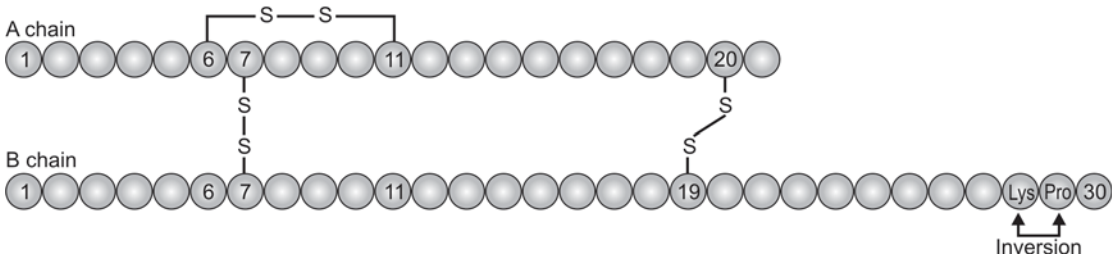

Fig. 1: Insulin Lispro

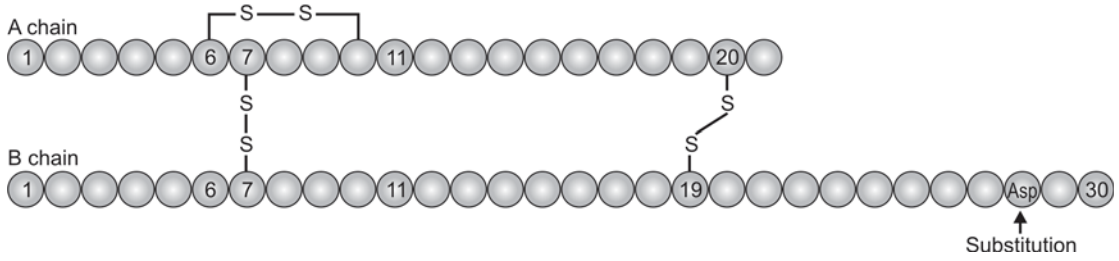

Fig. 2: Insulin Aspart

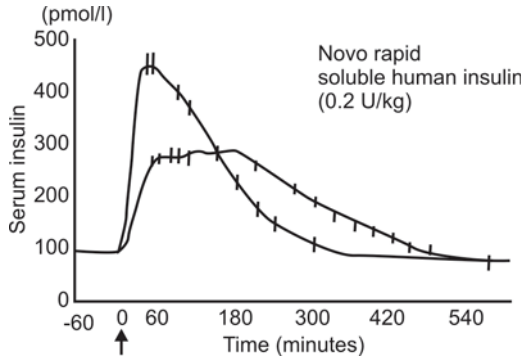

Fig. 3: A euglycemic clamp study in healthy volunteers showed that insulin aspart (NovoRapid) has 'twice as rapid onset and as high peak' than soluble human insulin[20]

Rapid Acting Analogues in Intensive Insulin Therapy

Intensive insulin therapy as a regimen is very poorly accepted by patients with type 1 diabetes practically because of the fear of hypoglycemia. Patients who were persuaded for tight glycemic control with intensive therapy, the benefits appear to be greater with more substantial and clinically useful fall in rates of major and nocturnal hypoglycemia. Heller, et al compared the effects of the rapid-acting insulin analogue insulin aspart and soluble human insulin on hypoglycemia and glycemic control in patients with Type 1 diabetes when injected immediately before meals as part of intensive insulin therapy. The rate of major nocturnal (24.00–06.00 h) hypoglycemic episodes was 72% lower with insulin aspart than with human insulin (0.067 vs. 0.225events / month; P = 0.001). The rate of minor events was also significantly reduced by 7% with insulin aspart (P = 0.048). It was concluded that the rapid acting insulin analogues appear to be strongly indicated for major nocturnal hypoglycemia[21].

Long-term Usage of Insulin Analogues

There have been scarce reports on long-term usage of insulin analogues. Long term diabetes trials such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UK PDS) showed that intensive insulin therapy resulted in the greatest reductions in HbA1c but was at the cost of an increased risk of hypoglycemia. Short term trials have shown that insulin aspart achieves similar or better HbA1c and does not adversely affect the hypoglycemia rate but there is also a lack of long term data regarding efficacy and safety with the use of rapid acting insulin analogues. In the only 3-year study existing for rapid acting analogues, the efficacy and safety of IAsp was compared to HI in patients with type 1 diabetes (n = 753). The duration initially was for 6 months and then extended to another 30 months. A total of 598 patients actually completed the study. The mean HbA1c, adjusted for country, baseline, and total daily dose, was 0.17 absolute percentage points lower with IAsp than HI (95% CI: -0.32 to -0.02, p = 0.028). The risk of major hypoglycemia did not differ between the two treatments[22].

Mitogenic Potential of Insulin Analogues

Insulin aspart binds to insulin receptor with similar affinity to human insulin, and to the IGF-1 receptor with slightly lower affinity. Insulin lispro binds to the IGF-1 receptor with affinity 1.5 × greater than human insulin[23]. Changes in the structure of the insulin molecule relative to human insulin may affect receptor interaction in unexpected ways. An increased residence time at the insulin receptor or an increased affinity for IGF-I receptors may increase the mitogenic potential of the analogue hormone; such pharmacological effects were associated with carcinogenicity in rodents with the prototype insulin analogue, Asp B10. This was the world's first insulin analogue but the development was stopped due to the unprecedented mitogenic potential.

Thus, concerns about the risk of cancer and retinopathy have been debated when insulin analogues have increased insulin receptor residence times or act as IGF-I receptor agonists. (Table 1) In the case of insulin detemir, the ratio of insulin receptor affinity to IGF-1 receptor affinity is not increased relative to insulin receptor affinity, and this is reflected in a low mitogenic

potency in a human cancer cell line. Insulin aspart has a favorable receptor binding affinity[23].

Table 1: Mitogenic potency of different insulins

	Insulin receptor affinity	*Metabolic potency*	*IGF-I receptor affinity*	*IGF-IR/IR affinity*	*Mitogenic potency (Saos/ B10 cells)*
Human insulin	100	100	100	1	100
Insulin aspart	92 ± 6	101 ± 2	81 ± 9	0.9	58 ± 22
Insulin glargine	86 ± 3	60 ± 3	641 ± 51	7.5	783 ± 13
Insulin detemir	18 - 46	~ 27	16 ± 1	0.9	~ 11
Insulin lispro	84 ± 6	82 ± 3	156 ± 16	1.9	66 ± 10

Usefulness of insulin aspart in renal impaired patients was done by Lyness, et al (2001)[24]. The study reported that absorption, distribution and clearance of insulin aspart were unaffected by renal impairment and that safety profile was comparable among persons with diabetes with various degrees of renal dysfunction.

Table 2: Duration of action of rapid acting analogues:

Insulin analogues	*Onset of action*	*Peak action*	*Effective duration*
Lispro	5-15 min	30-90 min	4-6 hr
Aspart	5-15 min	30-90 min	4-6 hr

Pharmacokinetics and Pharmacodynamics Issues of Rapid Acting Analogues

The pharmacokinetic and pharmacodynamic profiles of the rapid acting insulin analogues were studied by von Mach, et al (Table 2). This study compared the pk\pd profiles in fasting healthy males following a single subcutaneous injection of insulin lispro and insulin aspart. Insulin aspart was rapidly absorbed after subcutaneous injection as confirmed with lowest glucose concentration seen after 50 min of administration as compared to 60 min with insulin lispro (Fig. 4). The significance of the study is that a fast acting analogue like aspart may be advantageous for meal-related diabetes[25]. Clinically, the pharmacodynamic measure of the action of insulin is more indicative of its effect on blood glucose than is the pharmacokinetic measure.

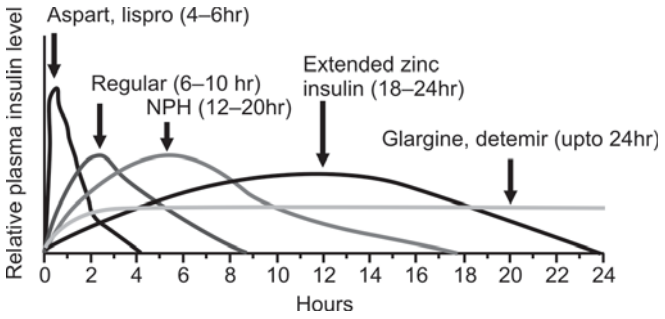

Fig. 4: Pharmacokinetic and pharmacodynamic properties of Insulin analogues

In a study of insulin aspart in which a dose of 0.2 unit per kilogram of body weight was used, the time to peak insulin action was 94±46 minutes for insulin aspart, as compared with 173±62 minutes for regular insulin ($P<0.001$)[26]. Use of these rapidly acting analogues also results in less variability in absorption at the injection site and possibly in less variation between and within patients[27].

Clinical Effectiveness of Insulin Analogues in Type 1 and 2 Diabetes Mellitus

Type 1 Diabetes

Except in the case of insulin-pump therapy, the two rapidly acting analogues are used only as prandial insulin replacement. Both insulin lispro and insulin aspart are superior to regular insulin in the reduction of postprandial hyperglycemia[28,29]. However, in general, studies involving multiple daily injections have not demonstrated that rapidly acting analogues improve glycosylated hemoglobin levels[30-33].

Though there have been published evidences of IAsp used postprandial for tight glycemic control, no study was done to establish the role of IAsp pre-prandial. Danne, et al, did a comparison study of the both and showed that glycemic control for postprandial treatment was not worse than preprandial treatment as assessed by fructosamine week 0 vs. 6 (mean ± SD, preprandial 367 ± 74 vs. 378 ± 90 µmol/l; postprandial 383 ± 83 vs. 385 ± 77 µmol/l) and HbA1c (preprandial 7.9 ± 1.3 vs.8.0 ±1.5%; postprandial 8.0 ± 1.4 vs. 8.3 ± 1.5%, P = 0.14). Relative risk of hypoglycemia (blood glucose <3.9 mmol/l) preprandially to postprandially was not significantly different between the groups. The conclusion stated, although preprandial administration of insulin aspart is generally preferable, this study showed that in children and adolescents, postprandial

administration of insulin aspart is a safe and effective alternative[34].

Type 2 Diabetes

For patients with type 2 diabetes in whom glibenclamide is not effective, the initiation of insulin therapy with insulin analogues taken at mealtimes was shown in one study to be more effective in improving HbA1c levels than was NPH insulin or metformin taken at bedtime[35].

Hypoglycemia: Comparison of Rapid Acting Insulin Analogues

The more rapid effects of insulin lispro and insulin aspart make postabsorptive hypoglycemia less of a problem with these analogues than with regular insulin[28-30,36,37].

A large meta-analysis that represented more than 1400 patient- years reported a 25 percent reduction in the frequency of severe hypoglycemia (i.e., that which required the assistance of another person to correct) with the use of insulin lispro, as compared with regular insulin[38].

Ferguson, et al assessed the potential of insulin lispro to limit the frequency of severe hypoglycemia without compromising glycemic control in a cohort of patients with type 1 diabetes who were at a high risk of severe hypoglycemia and compared the same with human insulin. Insulin lispro had an overall 47% lower incidence of nocturnal severe hypoglycemia[39].

Similar study profile was done by with insulin aspart and compared with human insulin. Heller, et al compared the effects of the rapid-acting insulin analogue insulin aspart and soluble human insulin on hypoglycemia and glycemic control in patients with Type 1 diabetes when injected immediately before meals as part of intensive insulin therapy. The rate of major nocturnal hypoglycemic episodes was 72% lower with insulin aspart than with human insulin[21].

It is not surprising that hypoglycemia occurs earlier with a rapidly acting analogue than with regular insulin[36,37]. The faster action of the rapidly acting analogues also alters the timing in terms of the risk of exercise-induced hypoglycemia. Patients who exercise early in the postprandial period (one to three hours after a meal) require a decrease in the insulin dose, whereas those who exercise later (three to five hours) require a smaller change or none[40].

Rapid Acting Insulin Analogues and Gestational Diabetes (GDM)

Recently insulin aspart was recently approved for use in pregnancy. The approval follows the results of the largest ever randomised controlled trial of modern insulin in pregnant women with type 1 diabetes. insulin aspart is the first modern insulin that has a label stating it can be used in pregnancy in the European union. The trial, which involved 322 pregnant women with type 1 diabetes and lasted more than four years, revealed that insulin aspart significantly improves postprandial glycaemic control in the first and third trimesters compared to human insulin. The risk of major hypoglycemia was 28% lower for patients treated with insulin aspart than human insulin. Risks of major (nocturnal and diurnal) hypoglycemia were 52% and 15% lower with insulin aspart than for human insulin. The trial showed that, when compared to human insulin, insulin aspart improved outcomes for both mother and child in terms of: fewer preterm deliveries ($p<0.053$), reduced risk of neonatal hypoglycemia requiring treatment, consistently lower rates of major hypoglycemia (24 hour, nocturnal and daytime) and reduced risks to the fetus, with outcomes comparable to human insulin. This study concluded that insulin aspart is at least as safe and efficacious as human insulin in pregnant women with Type 1 diabetes. The benefit to risk ratio is favorable for use of insulin aspart in pregnant women with diabetes[41].

CONCLUSION

Rapid acting insulin analogues were the first modern insulins to be made available for clinical use. They were designed by minor structural alterations in the aminoacid sequence of human insulin which reduced the forces of association between neighbouring insulin molecules. This led to the insulin being readily available as monomers upon subcutaneous injection leading to a rapid rise in blood levels. The improved pharmacokinetic profile overcame the limitations of conventional human insulin viz., meal-related constraints in administration, poor control of immediate post-meal glucose surges and snacking to avoid hypoglycemia. There is adequate clinical data available on efficacy and safety of rapid-acting analogues in both type 1 and type 2 diabetes. The rapid-acting analogues have now been approved for use in children above two years. There appears to be a place for these modern insulins in special situations like pumps and also in hospitals for treating

patients with renal dysfunction. The manufacturers have provided data on both stability and compatibility with intravenous fluids. Recently insulin aspart has also been approved for use in pregnancy.

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