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Comparative efficacy of humalog mix 75/25 with human Insulin.

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Abstract:

The study is designed to compare the postprandial glucodynamic profile of humalog mix 75/25, a new premixed insulin analogue containing 75% neutral protamine lispro and 25% insulin lispro with that of human insulin 70/30 in patients with type 2 diabetes mellitus.

Insulin lispro mix 75/25 is the first available insulin formulation in which both the rapid-acting and basal components are insulin analogue. Eighty four patients with type 2 diabetes participated in this study and were randomly assigned to 1 of 2 treatment sequence groups. Patients received an identical test meal on 4 occasions, completing 2 test meals for each treatment. Equal doses of mix 75/25 or 70/30 were administered 5 minutes before each of the 2 test meals, with doses individualized for each patients. Blood samples were collected for 4 hours after the meal for measurement of plasma glucose. Because of significant differences in the baseline fasting plasma glucose level between mix 75/25 and 70/30 of these parameters provide a truer comparison of the glucodynamic response between insulin formulations. Mix 75/25 resulted in significantly lower values compared eith 70/30. In patients with type 2 diabetes mellitus pre meal injection of mix 75/25 resulted in better post prandial glycemic control than did pre meal injection of 70/30 in the 4 hours after a standard meal. Mix 75/25 is a valuable option for managing post prandial blood glucose in patient with type 2 diabetes mellitus who require insulin.

Key-words: Humalog mix 75/25, insulin 70/30, Diabetes Mellitus.

Introduction:

All insulins have several anabolic and anti-catabolic actions on many tissues in the body. In muscle and other tissues (except the brain), insulin causes rapid transport of glucose and amino acids intracellularly, promotes anabolism, and inhibits protein catabolism. In the liver, insulin promotes the uptake and storage of glucose in the form of glycogen, inhibits gluconeogenesis, and promotes the conversion of excess glucose into fat. For patients with type 2 DM who require insulin therapy, achieving optimal glycemic control often requires an insulin regimen containing both basal and prandial insulin components. [1]

Insulin analogues are synthetic insulins with small changes in the amino acid sequence made in order to attain better pharmacokinetic characteristics. Both long-acting and rapidacting analogues with these characteristics have been developed. Premixed insulin analogues consist of a mixture of a rapid-acting insulin analogue and a slower-acting protaminated form of the analogue in various proportions, to provide both basal and prandial insulin effects in a single injection. Although available in vials, insulin analogue preparations are also available in pen devices to make their use simpler and more discreet for patients, as well as decrease dosing errors.

Compared with self-mixed insulins, premixed insulin formulations contain basal and mealtime insulin components, offer convenience and greater dosing accuracy, and play an important role in the treatment of patients with type 2 DM. [2] Insulin lispro is an insulin analogue that is rapidly absorbed after SC injection such that the time-action profile closely mimics the early phase of insulin secretion that is typically diminished in type 2 DM.[3] Premixed insulin formulations containing insulin lispro include insulin lispro 75/25 (75% neutral protamine lispro [NPL] and 25% insulin lispro) and insulin lispro mix 50/50 (50% NPL and 50% insulin lispro). The distinct time-action profiles of the insulin lispro component (rapid acting) and the protamine suspension component

(intermediate acting) are maintained within these mixtures. [4]

Table-1: Comparison between Humulin Mix 75/25 and Humulin Mix 70/30

Parameters	**Humulin Mix 75/25**	**Humalog Mix 70/30**
Onset	0.5 hrs	0.25 hrs
Peak	2.4 to 0.8 hrs	2.4 to 2.1 hrs
Duration	4 to 6 hrs	4 to 6 hrs
% of total activity occurring in first 4 hrs	45% to 25%	35 % to 18%
Administration	Immediately or within 10 to 15 minutes before a meal	10 to 15 minutes before or immediately after meals
Components	70% insulin aspart protamine and 30% insulin aspart	75% lispro insulin protamine and 25 % insulin lispro
Amino acid sequence	Amino acid proline by aspartic acid in position B28	Amino acid in position 28 to 29 position reversed
Mixing with other insulin	NO	NO
Route of administration	SC	SC

Several premixed fixed-ratio insulin preparations containing LP and NPL (an LP-based intermediate acting insulin) have been developed. These preparations include a premixed formulation consisting of a high proportion of LP (75% LP/25% NPL; H) and a premixed formulation consisting of a medium proportion of LP (50% LP/50% NPL; M). Glucose clamp and test-meal studies have demonstrated that these formulations maintain the rapid action of LP and that NPL has an activity profile similar to that of NPH. [5]

The insulin lispro molecule within the humalog formulation is a rapid-acting insulin analogue with a lower tendency for self-association than regular human insulin.It has a rapid absorption rate with a short duration of activity.These characterstics result in better postprandial glucose control and a lower risk of hypoglycemia compared with regular human insulin. Thus insulin lispro provides a more physiologic mealtime insulin profile than dose regular human insulin. Compared with regular human insulin in patients with type 1 diabetes mellitus (DM), LP has been shown to limit postprandial blood glucose (BG) excursions and to reduce the risk for hypoglycemia, primarily during the night.[6] However, because of the relatively short duration of action of LP (~4 hours), the BG concentration may increase during the late postprandial period (4–7 hours after meals) unless careful attention is paid to the replacement of basal (intermediate- or long-acting) insulin or to the basal insulin

infusion rate in patients using continuous SC insulin infusion.[7]

Humalog® Mix75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection, (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent. Chemically, insulin lispro is Lys(B28), Pro(B29) human insulin analog, created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. Insulin lispro is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce insulin lispro. Insulin lispro protamine suspension (NPL component) is a suspension of crystals produced from combining insulin lispro and protamine sulfate under appropriate conditions for crystal formation. (Table-1) represents the Comparison between HUMULIN MIX 75/25 and HUMULIN MIX 70/30.

Methodology:

This multicenter, randomized, open-label, 2-period crossover study was conducted at 3 different hospitals in North India. Approval of the protocol was obtained prior to patient enrollment.

Patients and study design

Eighty four patients aged 38-74 years, with type 2 diabetes mellitus were enrolled from hospital in the study. Patients were Included if they had type 2 diabetes mellitus but were otherwise healthy and in stable glycemic control, as determined by a glycosylated haemoglobin, A value =<1.5 times the upper limit of normal at a local laboratory. For >=30 days before entering the study, all patients had to be using a manufactured or self-prepared human insulin mixture in the morning, a short acting insulin at dinner and a second NPH insulin dose either at dinner or seoerately at bedtime.The total daily insulin dose had to be<=2.0 U/Kg.

Patients were not allowed to use oral antibiotic agents or glucocorticoids<=2 weeks of enrollment and were prohibited from using ultralenete insulin. Body mass index was required to be <=35 kg/m2 for entry into the study. Woman who were pregnant or lactating were excluded.

Patients were asked to maintain a stable body weight throughout the study and a similar pattern of physical activity on the day before each test meal. Patients were asked to keep the time of their usual evening insulin dose and meals consistent on the evening before the test meals. The bedtime insulin dose had to be given before 10 pm.

Many patients treated with insulin use mixture of short and intermediate-acting insulins. These mixtures are administered from separate vials in the same syringes or as 2 separate injections in patients using insulin pen devices.The use of premixed insulins is convenient for patients who administer similar ratios of individual insulins; premixed insulins also facilitate the use of insulin pen devices. In addition, accuracy of dosing can be improved with the use of insulin premixtures.

Post prandial glucodynamic reponse to either mix 75/25 or 70/30 after receipt of a standardized test meal patients received an identical test meal on 4 occasions and thus completed 2 test meals each for mix 75/25 and 70/30.

During the 2 week lead in period patients completed 2 practice test meals at home using 70/30 to determine the appropriate insulin dose for the 4 test meals. Patients recorded practice test meal information and blood glucose values after the meal until dinnertime.

Each patient was randomly assigned to undergo 2 test meals with mix 75/25 followed by 2 test meal with 70/30 or to

receive the treatment in the opposite sequence. Each test meal was separated by 3 to 11 days. For all the test meals, the study insulin was injected in the abdominal region 5 minutes before the test meals. The patient specific insulin dose was determined by the patient and the investigator based on the patient's blood glucose response to the 2 practice test meals. The doses of each study insulin were held constant across all 4 study test meals for each patient. Patient continued to use their usual regimens between visits.

On the morning of each scheduled study test meal, patients checked their blood glucose level. If their fasting blood glucose level was <5 or > 11mmol/L, their test meal visit was re-scheduled. If the value was >=5 and <=11, patients continued fasting omitted their usual morning insulin dose, and travelled to the investigative site.

The study insulin was then injected 5 minutes before the test meal .The test meal served immediately after the time 0 blood sample collection, and the meal consumed within 10 minutes. Additional blood samples were collected every 15 minutes up to 4 hours after the dosing. Four hours represents a typical between meal period.

If hypoglycemia(defined as a blood glucose level<3.5 mmol/L) or symptoms consistent with hypoglycemia occurred at any time during the test meal procedure a final blood sample was collected and the procedure terminated. All subsequent blood glucose values were treated for hypoglecemia with appropriate measures, were allowed to remain in the study and were scheduled for the remaining tests meals.

Results:

A total of 84 patients were enrolled (48 men, 36 women; mean [SD] age, 59 [11.2] years) (Table 2). No significant treatment-by-investigator interactions were noted. Two patients discontinued due to hypoglycemia condition the remaining 82 patients received study insulins. Three patients discontinued the due to medication problems and 4 patients discontinued the study total number of patients participated in the full study are 75 patients.

In the study the post prandial records obtained from Humalog mix 75/25 were more improved than the Humulin mix 70/30. (Table-3)

Discussion:

In a recent study serum glucose levels and responses to insulin were assessed in 22 patients with type 2 diabetes mellitus who received insulin lispro mix 75/25.Human insulin 70/30 and NPH insulin 10 minutes before a standard test meal. Insulin lispro mix 75/25 significantly lowered the maximum glucose and 4-hours glucose compared with 70/30. [8]

The magnitude of the reductions in postprandial blood glucose in the present study are similar to those in the earlier study. The improved postprandial glycemic control observed in the present study was also demonstrated by the result of clinical trials comparing mix 75/25 and 70/30.[9] In 1 trial involving 89 patients with type 2 diabetes mellitus mix 75/25 given twice daily resulted in improved 2-hours postprandial glucose concentrations after the meal at which mix 75/25 was given.[8]

A second study involving 37 patients with type 1 diabetes and 63 with type 2 diabetes compared mix 75/25 with 70/30 administed before the evening meal.Roach et al 39reported improved evening 2-hours postprandial blood glucose control.[10]

The results of the present study coupled with the results of previous studies demonstrate that mix 75/25 provides improved postprandial blood glucose control compared with 70/30.The result of the united kingdom prospective diabetes

indicate the importance of good glycemic control in preventing or slowing the development of long term complications associated with type 2 diabetes mellitus. With multiple glucose excursions throughout the day associated with tradional eating patterns.

Further support for the importance of controlling postprandial hyperglycemia was shown in the diabetes intervention study.

Table 2: Common patient characteristics (Mean+/-Standard)

Sex	Male	48
	Female	36
Body weight(in kg)		81.2+/- 11.99
Age(in years)		59.2
Basal metabolic index(BMI) [kg/m^2]		29.1+/-3.52
Duration of diabetes (in years)		14.0+/-8.26
Duration of insulin therapy(years)		5.6+/-5.00

Table 3: Comparison between the two analogous.

Parameters	**Insulin Lispro Mix 75/25**	**Human Insulin 70/30**
fasting plasma glucose (nmol/l)	8.9+/-2.2	8.6+/-1.9
2 hour post prandial (nmol/l)	12.3+/-2.9	12.8+/-3.0

In that study analysis revealed that postprandial hyperglycemia was an independent risk factor for all-cause mortality in patients with type 2 diabetes. The increasing evidence supporting the importance of postprandial glycemic control makes the availability of humalog mix 75/25 a valuable treatment option for patients with type 2 diabetes mellitus who require insulin.[10]

In the study the post prandial records obtained from Humalog mix 75/25 were more improved than the Humulin mix 70/30. (Table-3)

The emergence of multiple insulin products has provided new opportunities to achieve diabetes control. However, the number of options has raised concerns about the optimal choices of products. Several new insulin and insulin analogue preparations are now available for clinical use. Used as prandial insulin (for example, insulin lispro, insulin aspart, or insulin glulisine) and basal insulin (for example, insulin glargine or insulin detemir), the analogues simulate physiologic insulin profiles more closely than the older conventional insulins.[11] The advent of recombinant DNA technology

made it possible to overcome limitations in the time-action profiles of conventional insulins. Insulin therapy must be individualized. Nevertheless, certain subgroups of patients with diabetes can be differentiated from each other according to the pattern of blood glucose changes during the day. With the advent of various insulin preparations, the pharmaceutical industry aggressively promotes products to fit the needs of most, if not all, patients with diabetes. Many factors affect postprandial hyperglycemia including the amount of carbohydrate ingestion and rate of absorption, the loss of early-phase insulin secretion, the rate of glucagon secretion, the effect of these hormones on glucose uptake in muscle, and suppression of hepatic glucose production. In patients with type 2 diabetes, intermediate- or long-acting insulin may be added to existing oral antiglycemic agents to control fasting blood glucose levels. In the study the two marketed product HUMALOG MIX 75/25 and HUMALIN MIX 70/30 is taken and the post prandial records of the 84 patients are checked in the ideal condition and it is analysed through the study that the product HUMALOG MIX 75/25 gives more reduced post prandial glycemic records than the HUMULIN MIX 70/30.

Conclusion:

In patients with type 2 diabetes mellitus pre meal injection of mix 75/25 resulted in better post prandial glycemic control than did pre meal injection of 70/30 in the 4 hours after a standard meal. Mix 75/25 is a valuable option for managing post prandial blood glucose in patient with type 2 diabetes mellitus who require insulin.

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