Brief Communication

High-mix insulins

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ABSTRACT

Premix insulins are commonly used insulin preparations, which are available in varying ratios of different molecules. These drugs contain one short- or rapid-acting, and one intermediate- or long-acting insulin. High-mix insulins are mixtures of insulins that contain 50% or more than 50% of short-acting insulin. This review describes the clinical pharmacology of high-mix insulins, including data from randomized controlled trials. It suggests various ways, in which high-mix insulin can be used, including once daily, twice daily, thrice daily, hetero-mix, and reverse regimes. The authors provide a rational framework to help diabetes care professionals, identify indications for pragmatic high-mix use.

Key words: Aspart, biphasic aspart, biphasic insulin, co-formulations, lispro, lispro mix, premix insulin

Introduction

Various insulin preparations are now available for the management of diabetes. These molecules can be used in various regimes, according to the needs and wishes of the patient. Premix insulins and insulin co-formulations are frequently used insulin preparations, which help to manage both fasting and postprandial glycemia. These insulins can be classified according to the percentage of short-acting and long-acting insulin content [Table 1]. This communication reviews and suggests rational use of high-mix insulins which contain 50% or more than 50% of short-acting insulin.

Currently available premix insulins and co-formulations are listed in Table 1. These drugs contain one short- or rapid-acting, and one intermediate- or long-acting insulin. Of note, the high-mix category includes both biphasic human insulin 50:50 (BHI50) and 70:30 (BHI70), and analogue premixes: Biphasic aspart 50:50 (BI Asp50), lispro mix 50:50 (LM50), BI Asp 70:30 (BI Asp70), and LM 75:25 (LM75). The regimes that can be crafted with various high-mix insulins are listed and defined in Table 2.

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Clinical Data

Initiation and intensification with high-mix

The use of high-mix insulin has been supported and documented by a number of randomized controlled as well as observational trials. In a randomized open-label crossover study, (two 12-week periods) comparing LM50 with BHI50, mean 2 h postprandial glucose and 1-h postprandial glucose excursion were significantly lower in the LM50 group ($P = 0.004$ $P < 0.001$). Mean fasting glucose however was higher with LM50 ($P = 0.023$), hypoglycemia and adverse event rates were similar, but LM50 had the advantage of not requiring a long injection meal time gap.[1] Another group of researchers assessed the ability of BHI70, LM75, and LM50 to control of postprandial glucose level in type 2 diabetes, comparing their results with those of healthy, untreated individuals

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Table 1: Available premix and co-formulation insulins

Class	Ratio	Insulin
Co-formulation	30:70	Insulin degludec aspart (IDeg Asp)
Low premix	25:75	Biphasic insulin lispro (LM 25)
	30:70	Biphasic insulin aspart (BI Asp)
	30:70	Biphasic human insulin (BHI)
High premix	50:50	Biphasic insulin lispro (LM 50)
		Biphasic insulin aspart (BI Asp 50)
		Biphasic human insulin (BHI 50)
	70:30	Biphasic human lispro (LM70)
		Biphasic human aspart (BI Asp 70)
	75:25	Biphasic human insulin (BHI 70)
		Biphasic human lispro (LM75)

Table 2: High-mix regimes

High-mix regimes: Regimes using a single high-mix insulin
- Once daily
- Twice daily
- Thrice daily

Hetero-mix regimes: Regimes using more than one insulin preparation
- Twice daily: E.g., high-mix 50:50 with breakfast, premix 30:70 with dinner
- Thrice daily: E.g., high-mix 50:50 with breakfast and lunch; premix 30:70 with dinner

Reverse mix regimes: Regimes using low dose during day time, and high-mix at night
- Twice daily: E.g., premix 30:70 with breakfast, high-mix 50:50 with dinner

consuming similar test meals (500 kcal, 50% carbohydrate, 34% fat, and 16% protein). In this single entire randomized study, conducted over four visits, the postprandial rise was most attenuated with LM50.[2] These studies underscore the benefits of using high-mix insulin in persons with postprandial hyperglycemia.

In a study on insulin-naïve type 2 diabetes patients, BHI 70:30 was used to initiate insulin therapy in persons not achieving glycemic control on two oral agents, and compared with addition of a third oral agent. At 24-week therapy, a high-mix insulin (70:30) twice daily regime, in combination with metformin, was as effective as triple oral therapy in lowering both the A1c and fasting glucose. The high-mix regime was more cost-effective and associated with much lower discontinuation rates, whether due to lack of efficacy or lack of tolerability.[3]

In a 36-week long study in type 2 diabetes, twice daily BI Asp30 was compared with thrice daily BI Asp50 and thrice daily BI Asp70, all combined with metformin. After 12 weeks, 43% of BI Asp50 and 54% of BI Asp70 subjects switched their dinner insulin to BI Asp30. The BI Asp50 regime was found superior to the BI Asp30 regime in A1c lowering while both high-mix regimes were able to achieve significantly better postprandial glucose. Hypoglycemia was more frequent in the BI Asp70 arm.[4] A similar trial confirmed that a thrice daily BI Asp regimen can safely be used to intensify treatment for type 1 and type 2 patients inadequately controlled on twice daily BHI. In this multicenter open-label parallel group trial, the A1C and average blood glucose levels were significantly lower for the BI Asp treatment group compared with the BHI30 group (both $P = 0.0001$). Though intensification of insulin therapy with BI Asp thrice daily was associated with a higher risk of minor hypoglycemia (relative risk = 1.58, $P = 0.0038$), the overall rate of minor hypoglycemia remained low with both the BI Asp and the BHI treatments.[5]

LM50 injection thrice daily has been compared with BHI 30:70, used twice daily. This 24-week long crossover study showed better reduction of A1c ($P = 0.034$), baseline mean blood glucose ($P = 0.035$), and postdinner glucose ($P = 0.001$) with LM50.[6] A smaller study of 13 subjects also assessed control over 24 h with LM50 in patients who were poorly controlled on twice daily low-mix insulin (LM25, LM30). The authors found improved glucose control and lower glycemic variability with LM50 than with low-mix therapy.[7] In another open-label 16-week long randomized trial, the efficacy and safety of thrice daily LM50 were compared with the progressive titration of twice daily LM75 or BI Asp70, administered in combination with metformin. Both arms demonstrated a similar insulin dose requirement. The twice daily arm achieved lower fasting and postbreakfast glucose levels and a higher frequency of nocturnal hypoglycemia ($P = 0.0063$). The LM50 subjects had lower postlunch glucose levels and experienced more weight gain ($P = 0.0009$).[8]

A 24-week long randomized study of 374 subjects inadequately controlled with glargine and oral agents comparing thrice daily LM50 with a lispro-glargine based basal therapy found significant A1c reductions in both groups. A greater number of persons (69%) achieved target A1c <7% in the basal bolus group, as compared to the LM50 thrice daily arm (54%) ($P < 0.09$).[9] In a randomized open-label crossover study of 89 subjects with type 1 diabetes, two treatment regimens were compared over two 8-week periods: Lispro self-mixed with neutral protamine hagedorn (NPH) before meal plus NPH alone at bedtime, with preprandial high-LM (75:25) or medium LM (50:50), plus NPH alone at bed time. The mean postprandial values and A1c were similar in both groups. The incidence of hypoglycemia was lower in both groups, but relatively higher ($P < 0.05$) in the high-mix/medium-mix group. Most hypoglycemic episodes occurred between 12 pm and 6 pm.[10]

In an observational trial lasting 26 weeks, patients on BI Asp30, 50 or 70 were analyzed for efficacy and safety. Of the 592 type 2 diabetes patients being treated with BHI30 or

BHI50 with or without oral agents, 72% switched to twice daily BI Asp and 20% to thrice daily BI Asp. A1c improved over 26 weeks ($P < 0.001$), while there was no increase in hypoglycemia. About two-thirds of all patients were on BI Asp30, and one-third were on BI Asp50. Very few patients took BI Asp70. This observational trial suggests patterns of prescription premixed insulin that would be appropriate for an average practice.[11]

Hetero-mix Regimes

Hetero-mix regimes, that is, using one premix combination with the morning meal and a different premix combination with the evening meal, have also been studied. Another hetero-mix regime that can be used in a thrice daily prescription includes high premix with breakfast and lunch, and low premix with dinner.

The effect of a "hetero-mix" regime using biphasic insulin aspart high-mix (70:30) before breakfast and lunch along with biphasic insulin aspart 30:70 with dinner has been compared with BHI 30:70, used twice daily. In this 60-days long open-label crossover study, 38 subjects received both treatments for 30 days each. Average serum glucose concentrations over 24 h were similar in both groups. However, daytime average glucose concentration was lower with the BI Asp regime ($P = 0014$), as was mealtime serum glucose excursion ($P = 0.000$). The total daily dose of the high-mix based regime was 110% that of BHI, but the incident of hypoglycemia was similar.[12]

To compare the efficacy of two different high-mix insulin regimes, a randomized double-blind crossover study was performed on 16 subjects with type 2 diabetes over two 4-week periods. Thrice daily high-mix aspart (70% protaminated aspart, 30% aspart) was compared with another strategy of prescribing before breakfast and lunch along with BI Asp50 (50% protaminated aspart, 50% aspart) before dinner. Daytime average glucose and postprandial glucose excursions were lower with the thrice daily high-mix treatment as compared to the run-in period (of treatment with twice daily BHI), ($P < 0.05$), but fasting glucose levels were higher. Switching dinner dose to BI Asp50 did not significantly affect the overall glycemic control. The authors suggested replacement of dinner dose with a low-mix insulin to achieve optimal glycemic control.[13]

Progressive Intensification with High Premix Insulin

A protocol employing a progressive approach with high-mix therapy, studied a regime beginning with once daily LM50, and progressing to twice daily LM50, then thrice daily LM50. Dinnertime insulin LM 50/50 could be replaced with insulin LM 75/25 if needed for fasting glycemic control. This was compared with conventional basal plus and basal bolus therapy using glargine and lispro. In this treat to target study of 484 subjects, which lasted 36 weeks, mean A1c achieved was similar in both arms. No difference in hypoglycemia was noted.[14]

In a similar designed Japanese study, using stepwise introduction of LM50 in type 2 diabetes patients, inadequately controlled on oral therapy, this method of treatment was found to be safe and effective. Of the 116 completers, 9 patients reminded on once daily, 21 on twice daily, and 86 on thrice daily LM50. By the end of the 48-week long study, 52.6% of all 135 patients were able to achieve target A1c <7.4%, without having suggested specific target fasting glucose values, or dosing algorithms, to participating investigators.[15]

Clinical Indications

The need for mid ratio and high-ratio premix insulin has been reviewed earlier.[16,17] These preparations are well-tolerated. Though the frequency of minor hypoglycemia is higher with these agents, the risk of nocturnal hypoglycemia is less. Their ability to address postprandial hyperglycemia makes them a useful addition to the conventional (low ratio) premixed formulations. Objective indices have been developed to measure the contribution of postprandial hyperglycemia to overall glycemic status. These include the postprandial glycemic excursion (PPGE), prandial fasting index (PPGE/fasting plasma glucose [FPG]), and A1c prandial product (A1c × PFI). Conversely, the FPG/A1c ratio suggests the contribution of fasting glycemia to the overall glycemic burden.[18]

Indications for the use of high premix are listed in Table 3. The objective indications for high premix include persons with postprandial hyperglycemia, not responding to conventional or low premix insulin. Such a situation is seen in persons who have high carbohydrate/fat-containing, or relatively large meals, consumed at relatively lesser frequencies. This is common in many communities and professions, where religious/social or workplace concerns do not allow intake of small frequent meals.

High-premix insulins may be used as an initial injectable therapy in persons who take heavy meals, or exhibit pronounced PPGEs. More often than that, they are used to intensify insulin therapy in persons who do not respond

Table 3: High-mix regimes and indications

Regimes	Indication	
	Glucocentric	Dietary
High mix		
Once daily	One meal with high PPGE	One heavy meal
Twice daily	Two meals with high PPGE	Two heavy meals
Twice daily	Inadequate response to twice daily low premix/high premix	Three heavy meals
Hetero-mix regime, twice daily		
High-mix AM	High PPGE with low mix twice daily	Heavy breakfast; normal lunch and dinner
Low mix PM	High fasting glucose with high-mix twice daily	
Hetero-mix regime, thrice daily		
High-mix AM, noon	High PPGE with low mix thrice daily	Heavy breakfast and lunch
Low mix PM	High fasting glucose with high-mix thrice daily	
Reverse mix	High PPGE postdinner; low PPGE postbreakfast	Heavy dinner; Ramadan

PPGE: Postprandial glycemic excursion

adequately to low-mix insulin and are unwilling to increase the frequency of injections. Hetero-mix regimes provide the advantage of safe 24 h control in persons who do not respond adequately to either low premix twice daily, or high premix twice daily. The hetero-mix regimes leverage the potent prandial glucose reducing property of high-mix, and the safe reduction in fasting glycemia achieved with low-mix insulins. High-mix prescribed during daytime achieves adequate postprandial control while low-mix administered with the night time meal achieves glycemic control with minimal risk of nocturnal hypoglycemia.

High-mixes also find use in certain communities where religion demands adherence to strict dietary patterns. The Jain community of India, for example, fasts daily from dusk to dawn. A twice daily high-mix regime, at breakfast and lunch, with or without low-dose and low-mix insulin at supper, often serves well. Other patients do well on a simpler hetero-mix regime of high with breakfast, and low-mix with supper.

Usage in Ramadan

During Ramadan, a reverse hetero-mix regime, using low-mix at Suhur (predawn meal) and high-mix at Iftar (postdusk meal), allows good glycemic control, with minimal risk of hypoglycemia during the daytime fasting period. Practical guidelines published on the use of low premix insulin during Ramadan[19] can be used to adjust doses of high-mix insulin as well.

The key to achieving optimal control during Ramadan is an active interaction between the patient and their healthcare providers. Ideally, the patients should have their therapeutic regime assessed by their providers in the weeks just prior to Ramadan. In the event a therapy change is required, it is recommended to try it out prior to the actual start of Ramadan to help make any necessary adjustments. In addition to that, proper dietary advice is essential.

Some patients want to continue with the same regime of low-mix insulins as they have been using it for a long time. In such cases, regular monitoring of self-monitoring of blood glucose is recommended to make the necessary adjustments in both the insulin dose as well as the diet.

Some individuals take an additional early morning meal usually around midnight. This makes it the third meal between the usual dusk time and predawn meals. In this instance, a single shot of a short-acting analog may be needed to counter the ensuing hyperglycemia.

Posology

High-premix insulin can be used in a once daily, twice daily, or thrice daily regime. The choice of dosage frequency will depend on glycemic profiles and meal patterns. The initial dose is usually 0.2 units/kg body weight/day but can be up-titrated at regular intervals, as per requirement. Postmeal glucose values are used to assess the adequacy of the short-acting component, while premeal glucose, preceding the next meal, is measured to assess the effect of the long-acting insulin. The average dose distribution for a twice daily high mix regime is 50:50. In patients who need three doses for control, the average distribution is 50% with breakfast, 15% with lunch, and 35% with dinner. However, this may vary based on individual or regional dietary habits.

Conclusion

The high-mix insulin preparations are a useful therapeutic modality that has a definite utility in the management of diabetes. They combine rapid-acting and long-acting insulins to achieve both prandial and fasting glucose. They can be used in once daily, twice daily, and thrice daily doses, for initiation, as well as intensification of therapy. When prescribed to patients with appropriate dietary and glycemic profiles, high-mix insulins help to achieve safe, well-tolerated, and effective glycemic control.

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Conflicts of interest

There are no conflicts of interest.

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