Recent advances in premixed insulin
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Abstract
Premixed biphasic insulin is the most commonly prescribed insulin in Pakistan, as well as in neighbouring countries. This article describes the rationale of using premixed insulin both for initiation and intensification, the evidence in its favour, and the guidelines supporting its use. The review discusses recent advances in the field of premixed insulin, especially insulin degludec aspart combination.

Keywords: Premixed insulin, Pakistan.

Introduction
Insulin regimes are classically classified as basal, prandial and basal-bolus.1 The combination of basal and basal-bolus insulin in the same regime, in ratios suited to the individual patient, is known as a split-mix regime. Developments in pharmaceutics allowed the production of premixed biphasic insulin in pre specified ratios. While a wide variety of ratios was available earlier, few premixed insulins are available worldwide now.2 Some of these are listed in Table. This review article describes the pharmacology of premixed insulin, and covers recent advances in this field. While insulins premixed with glucagon-like peptide 1 receptor are also under development,3 they will be the topic of a separate article.

Table: Available premixed insulins.

<table>
<thead>
<tr>
<th>Name</th>
<th>Prandial component</th>
<th>Basal Component</th>
<th>Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic insulin(BHI)</td>
<td>Regular insulin</td>
<td>NPH insulin (neutral protamine Hagedorn)</td>
<td>30:70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50:50:00</td>
</tr>
<tr>
<td>Biphasic insulin aspart(BIAsp)</td>
<td>Insulin aspart</td>
<td>Protaminated aspart</td>
<td>30:70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50:50:00</td>
</tr>
<tr>
<td>Biphasic insulin Lispro(BiLis)</td>
<td>Insulin lispro</td>
<td>Protaminated lispro</td>
<td>25:75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50:50:00</td>
</tr>
<tr>
<td>Insulin Degludec + Aspart (IDegAsp)*</td>
<td>Insulin aspart</td>
<td>Insulin degludec</td>
<td>30:70</td>
</tr>
</tbody>
</table>

Rationale
In a normal, healthy person, about 50% of endogenous insulin is secreted from the pancreas in a basal manner, meant to ensure fasting euglycaemia. The other half is secreted as boluses, in response to meals, and is targeted at maintaining postprandial euglycaemia.

Physiological insulin replacement, therefore, requires exogenous provision of both basal and prandial insulin.4 This has conventionally been done using a basal-bolus regime, consisting of 3 bolus and 1-2 basal injections.5 This regime has the advantage of being 'physiological', but is certainly not convenient for the patient who has to take frequent injections, coupled with meals at regular intervals.5 Basal-bolus regimes may not be as necessary for persons with type 2 diabetes, as they are for those with type 1 diabetes. This is because most type 2 diabetes patients continue to secrete some amount of residual insulin, which is enough to prevent severe hyperglycaemia and ketosis.6

To reduce the number of injections required per day, the split-mix regime was developed. This involved mixing required doses of regular insulin and intermediate insulin (Lente or NPH) in the same syringe, immediately prior to injection. Acceptance of this therapy, along with improvements in insulin manufacture, allowed the creation of pre-mixed biphasic insulin. Such insulins provide variable ratio of intermediate acting insulin (to provide basal coverage) and regular insulin (to provide prandial cover).
Further Evolution
The invention of insulin analogues, specifically aspart and lispro, has allowed them to be combined with protaminated aspart and lispro, respectively. The favourable pharmacokinetic properties of these molecules has added flexibility, safety and convenience to premixed regimes. Premixed analogues have also been tried as once-daily and thrice-daily regimes; for initiation as well as for intensification. Such research has expanded the utility of these drugs, coupled with greater understanding of the benefits of insulin therapy.

Initiation With Premixed Insulin: Once Daily
Various studies have explored the efficacy of premixed insulin as a treatment for insulin-naïve patients.

A randomized controlled trial conducted in 15 countries found that once daily premixed aspart insulin was clinically equivalent to insulin glargine in reducing HbA1c. A post-hoc analysis of subjects from the three Asian countries (India, Malaysia, and the Philippines) however, revealed that premixed insulin, given once daily, had efficacy superior to that of basal insulin, given once daily.

In the 1-2-3 study, 41% of all subjects were able to achieve target HbA1c with once daily premixed aspart. Similar results are noted in studies carried out in primary care settings which have demonstrated that patients are able to safely self-titrate their dose requirements of premixed insulin.

Initiation With Premixed Insulin: Twice Daily
Premixed insulin has traditionally been perceived as twice-daily insulin, and can be initiated as such. While ample research has been done using this regime, the Initiate Plus Trial proved that in the primary care setting, self-titration of premixed aspart, even with minimal dietary counseling, helped over 40% of subjects achieve target HbA1c.

Intensification With Premixed Insulin
Premixed insulin can be used for intensification of therapy as well, if the initiation regime of once or twice daily injections is unable to achieve target. The 1-2-3 study showed the efficacy and safety of using premixed aspart insulin in once daily, twice daily and thrice daily doses. Targets were achieved in 41%, 70% and 77% subjects, respectively.

Posology
Premixed insulin, if prescribed once daily, should be offered with the main meal of the day. The choice of timing of administration may also be made based upon the meal which shows the highest post prandial glucose excursion.

If taken twice daily, premixed insulin is usually prescribed with breakfast and with dinner. Human insulin is started in a 2:1 ratio, with two thirds of the total daily dose at breakfast, and one thirds at dinner. Human premixed insulin is ideally injected thirty minutes before a meal. Premixed analogue insulin, i.e., biphasic aspart and biphasic lispro, are often prescribed in a 1:1 ratio, with 50-60% of the dose at breakfast, and 40-50% at dinner time. Biphasic analogue insulins allow flexibility in time administration: they can be injected before, during or after a meal, without impact on efficacy, or on risk of hypoglycaemia.

Dual Premixed Insulin Regimes
Persons who consume a heavy breakfast (parathas, for example), may benefit from a dual premixed regime. Such regimes involve the use of a 50:50 mixture (human, aspart or lispro) at breakfast, and a 30:70 or 25:75 mixture at dinner.

An inverted dual regime (a 30:70 or 25:75 mixture at breakfast, and a 50:50 mixture in evening) can also be used during Ramadan. The relative dose distribution of insulin may also change during Ramadan. A common practice is to reduce the morning dose of insulin by half.

Premixed Insulin In Type 1 Diabetes
The most physiological subcutaneous insulin replacement for people with type 1 diabetes is the basal-bolus regime. However, various psycho sociocultural realities have to be taken in to consideration while crafting an insulin prescription.

Some children and adolescents may be unable to, or unwilling to, accept 4 to5 insulin injections per day, because of various practical reasons. Such patients can be prescribed premixed insulin, while being explained the limitations of this regime. Premixed insulin twice daily can also be combined with rapid acting insulin at lunch time to achieve better control, with only 3 injections as compared to 4-5 injections in a basal-bolus regime.

Premixed Insulin and Oral Hypoglycaemic Agents
Premixed insulin can be combined with various oral hypoglycaemic drugs for better control. Metformin, alpha-glucosidase inhibitors (acarbose, voglibose),
dipeptidyl peptidase-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin) can be used safely with insulin. All these drugs have an insulin-sparing effect, and if used appropriately, may help reduce insulin requirement.

Secretagogues can be used in combination with insulin in specific clinical situations. Premixed insulin, taken as a once daily dose, can be combined with a sulfonylurea, taken with the ‘antipodal’ meal. Premixed insulin, taken twice daily, can be combined with a short acting secretagogue such as repaglinide, administered at lunch time.

**Novel Premixed Combination: Insulin Degludec-Aspart**

Recently, the first premixed co-formulation of two insulin analogues has been approved in Europe and other countries. Insulin degludec- aspart (IDeg Asp) is a combination of the ultra-long acting basal insulin degludec, and rapid acting aspart. It is able to achieve good glycaemic control with a lower risk of hypoglycaemia. The advantage of IDeg Asp is that it can be combined with two injections of aspart, to create an effective three dose regime. It can also be used as once daily or twice daily insulin. Its basal component, degludec, has been reviewed earlier in the JPMA.

**Premixed Insulin: Guidelines**

Guidelines of the International Diabetes Federation (IDF), and American Association of Clinical Endocrinologist (AACE) recommend premixed insulin as a therapy for insulin initiation. Guidelines from other South Asian nations, Bangladesh and India, clearly encourage premixed insulin for initiation of treatment. The AACE guidelines make a categorical statement in favour of insulin analogues, based upon their superior safety profile.

**Premixed Insulin in Pakistan**

Real life data regarding insulin usage and preference is available from Pakistan. The results from the A1chieve study prove that switching therapy to insulin analogues such as BIAsp 30 would be beneficial in achieving target glycaemic control with a low incidence of hypoglycaemia.

**Conclusion**

Premixed insulin is an effective and safe treatment option, which lends itself to use in versatile manners. It is convenient to use for people with diabetes, easy to explain for diabetes educators, and pragmatic to prescribe for physicians. Its popularity in Pakistan and neighbouring countries speaks for its utility. Availability of newer premixed insulin such as IDeg Asp will further expand the utilization of premixed insulin.

**References**

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