Insulins: Basal or premix insulin in type 2 diabetes management

When and how to introduce insulin

KEY MESSAGES

- Premixes/admixes of regular and NPH/lente insulin in the same syringe should never be used in type 1 diabetes patients’ or in type 2 diabetes of long duration targeting an HbA1c level of less than 7%.
- Analogue premixes are the most popular insulins worldwide, but they also result in inadequate prandial insulin delivery and excess inter-prandial supply.
- Premixes therefore increase the risk of hypoglycaemia, while achieving similar HbA1c levels as other insulin strategies.2,3
- With regard to the basal insulins, insulin detemir and insulin glargine – one is not superior to the other; but they are different and require different dosage regimens.
- Ultra-long-acting insulins are on the horizon – such as insulin degludec, glargine U300 (concentrated insulin glargine) and LY2605541 (pegylated insulin lispro).
- Where NPH insulin is used as the basal insulin, explore opportunities to optimise therapy by (i) reducing risk of nocturnal hypoglycaemia with self-monitoring protocols and a bedtime snack (ii) splitting the dose every six hours and, in patients with lower BMIs, not up-titrating too aggressively.

Poor control of type 2 diabetes and blood glucose levels occurs over time due to progressive loss of β-cell function. “The UKPDS study,” which has provided key insights, was undertaken with older oral drugs (chlorpropamide, glibenclamide and metformin, along with lifestyle measures), yet I am unsure as to whether we...
can prevent progressive deterioration with the new oral agents,” Professor Bolli said. “However, what is true then is true today: at the time of diagnosis of type 2 diabetes, the hidden history of developing diabetes has resulted in significant loss of pancreatic β-cell function. This means that we should be aggressive in terms of treating type 2 diabetes at the time of diagnosis.” Referring to the recent ADA/EASD guidelines for treating type 2 diabetes, Professor Bolli pointed out that the addition of insulin to metformin at stage 2 of intensifying type 2 diabetes treatment would be the focus of his presentation.

How do we start and progress with insulin treatment?
The major focus of insulin therapy is to treat the dysfunctional glucose control and restore insulin function to physiological normality (Figure 1). “Glucose homeostasis in normal subjects is characterised by sharp insulin spikes with a return to basal insulin levels in pulses between meals (average plasma basal insulin levels are approximately 10 μU/ml),” Professor Bolli noted.

Initiation: Premixed insulins
Several studies have highlighted the limitations of premixed insulins, despite their universal use. “The premixes are rigid, non-flexible treatments; there is a greater risk of hypoglycaemia at the same HbA1c levels, with increased variability in dose-delivery due to the need to re-suspend NPH prior to injection,” Professor Bolli noted.

<table>
<thead>
<tr>
<th>Table 1. Hypoglycaemic events over 12 weeks in type 2 diabetic patients</th>
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<tbody>
<tr>
<td><strong>Major episodes</strong></td>
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<tr>
<td>Total number of episodes in type 2 patients</td>
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<tr>
<td>Minor episodes</td>
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<td>Total number of episodes in type 2 patients</td>
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“Premixes do not exist in nature, nor do they meet real insulin needs,” he said.

In a recent evaluation of the glycaemic profiles of premixed aspart 30/70 versus human 30/70 insulin as administered by 300 type 1 and type 2 diabetes patients to achieve HbA1c levels of 8%, the extent of hypoglycaemia late morning and late at night was evident. Major hypoglycaemic episodes were fewer with the analogue premix (BIAsp30), but the overall risk of hypoglycaemia did not differ significantly between the human and analogue premix. The risk of hypoglycaemia in type 2 diabetes on these therapies is summarised in Table 1.

In contrast, the INITIATE study of two BIAsp30 insulin doses versus insulin glargine showed that the premix could achieve better HbA1c levels than the basal insulin. “This, however, occurred at a cost of significantly more hypoglycaemic events than with glargine,” Professor Bolli pointed out.

Evaluating insulin initiation strategies
A very recent study evaluated three strategies – twice-daily premix, basal plus one rapid-acting prandial insulin and thirdly, basal-bolus with up to three prandial injections added. The HbA1c achieved with the premix and the basal-plus (glargine plus 1) was identical, but incident hypoglycaemia was very different after one year (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Incidence of hypoglycaemia (%)</th>
<th>&lt;3.9mmol &amp; symptoms</th>
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<tbody>
<tr>
<td>Premix</td>
<td>72</td>
</tr>
<tr>
<td>Basal plus 1</td>
<td>62.5</td>
</tr>
<tr>
<td>Basal plus 3</td>
<td>60.1</td>
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<tr>
<td>Overall hypoglycaemic event rate (event/ patient year)</td>
<td>(%)</td>
</tr>
<tr>
<td>Premix</td>
<td>12.2</td>
</tr>
<tr>
<td>Basal plus 1</td>
<td>7.1</td>
</tr>
<tr>
<td>Basal plus 3</td>
<td>7.2</td>
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“There was a doubling of episodes/patient-year with premix as compared to basal insulin plus three prandial injections – a rather unexpected finding.”
“In the now classic, 10-year-old study" comparing insulin glargine to NPH insulin mean HbA1c levels on treatment were similar, but hypoglycaemic events were significantly reduced with glargine, particularly nocturnal hypoglycaemia,” Professor Bolli pointed out.

Hypoglycaemia is serious and has serious consequences (Table 3).

With regard to basal insulins, Professor Bolli summarised his evidence-based views as:

- Insulin glargine and detemir are equally useful as basal insulins, but increased detemir doses are required in obese type 2 diabetes patients.
- NPH insulin is associated with more hypoglycaemic events than the analogue basal insulins

“The new longer-acting basal insulins will provide opportunities for better compliance from patients, but clinicians will need to assess their place in type 2 diabetes management as more data emerges from international trials,” Professor Bolli concluded.

Table 3. Harmful effects of hypoglycaemia

- Brain dysfunction
- Seizures and associated injuries, e.g. fractures
- Possible cause of long-term cognitive impairment in children
- In adults may provoke vascular events
- Possible mechanism for ‘dead in bed’ syndrome

References:
