Switching to Biphasic Insulin Aspart 30 in Patients Uncontrolled on Human Premix Insulin

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Abstract

Two cases relating to switching from biphasic human insulin 30 (BHI 30) to biphasic insulin aspart 30 (BIAsp 30) are described. Case 1: switching from BHI 30 to BIAsp 30 due to inadequate glycosylated haemoglobin (HbA\textsubscript{1c}) control. Case 2: switching from BHI to BIAsp 30 due to nocturnal hypoglycaemia. Case 1: HbA\textsubscript{1c} fell from 7.9 % with BHI to 6.9 % with BIAsp 30 at the six-month follow-up. Postprandial glucose (PPG) fell from 12.6 mmol/l with BHI to 9.1 mmol/l with BIAsp 30. Case 2: a man who had experienced recurrent nocturnal hypoglycaemia with neutral protamine Hagedorn (NPH) or BHI was able to maintain his glycaemic control without severe nocturnal hypoglycaemia with BIAsp 30. BIAsp 30 offers advantages over BHI 30 in terms of faster absorption, higher peak concentrations, and a more rapid and pronounced prandial glucose-lowering effect, which means that BIAsp 30 can improve PPG control and reduce the risk of nocturnal and major hypoglycaemic episodes.

Keywords

Biphasic human insulin 30 (BHI 30), biphasic insulin aspart 30 (BIAsp 30), fasting plasma glucose (FPG), HbA\textsubscript{1c}, insulin, postprandial glucose (PPG), type 2 diabetes

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Premix insulin analogues such as biphasic insulin aspart 30 (BIAsp 30) offer advantages over biphasic human insulin 30 (BHI 30) in terms of faster absorption, higher peak concentrations, a more rapid and pronounced glucose-lowering effect and comparable duration of action of the basal component.\textsuperscript{1,2}

The improved pharmacokinetics of BIAsp 30 versus BHI 30 mean that BIAsp 30 demonstrates significantly improved postprandial glucose (PPG) control and fewer nocturnal and major hypoglycaemic episodes, and it can be more conveniently dosed immediately before or following a meal.\textsuperscript{3–9} The following two case reports examine the effects of BIAsp 30 initiation on glycaemic control and on reducing problem hypoglycaemia in two patients on prior BHI 30 treatment.

Case Report 1 – Overweight Patient with an Above-target Glycosylated Haemoglobin

CD was a 56-year-old male who had been diagnosed with type 2 diabetes in 2003 aged 48. He had a history of being overweight and his most recent body mass index (BMI) measurement was 29.8 kg/m\textsuperscript{2} (body weight 88 kg). He was diagnosed with microalbuminuria in 2007. He was receiving concomitant medication for endothelial dysfunction including simvastatin, enalapril, thiazide and low-dose acetylsalicylic acid (aspirin).

Prior Diabetes Treatment

At diagnosis in 2003 he had a glycosylated haemoglobin (HbA\textsubscript{1c}) of 7.5 % (58 mmol/mol) and he was initiated on metformin monotherapy, which he continued until 2004. Between 2004 and 2008 he was treated with a combination of metformin and a sulphonylurea. In 2005 his HbA\textsubscript{1c} was stable at 7.4 % (57 mmol/mol); however, an HbA\textsubscript{1c} measurement of 8.5 % (69 mmol/mol) in 2008 prompted the decision to replace sulphonylurea with BHI. The addition of BHI resulted in a marked improvement in his HbA\textsubscript{1c}, which fell to 7.2 % (55 mmol/mol) in 2009. However, in 2010 his HbA\textsubscript{1c} had increased to 7.9 % (63 mmol/mol). A closer look at his fasting plasma glucose (FPG) and self-measured PPG showed that while his FPG had remained stable between 2009 and 2010 (5.2 mmol/l and 5.1 mmol/l, respectively), his PPG had increased from 9.4 mmol/l to 12.6 mmol/l.

Intervention

The decision to modify treatment was based on the increase in the patient’s HbA\textsubscript{1c}, reflecting poor PPG control with his current insulin regimen of BHI twice daily (38 and 30 units morning and evening). In discussing intensification options with the patient, it was clear that he was unwilling to consider basal–bolus regimens as he did not want to have to administer up to five insulin injections daily and was worried about the need for intensive glucose monitoring. The patient felt more
comfortable with premix insulin as it meant he could continue injecting twice daily, and was happy to monitor his pre-meal glucose levels to enable dose titration. BIAsp 30 was initiated at the same dose as his previous insulin treatment (38 units with breakfast and 30 units with his evening meal) and was titrated according to the standard titration algorithm. By six months the insulin dose had increased by 15–20%. This treatment switch reduced his HbA1c by approximately 1%, to 6.9% over the six-month follow-up, which was associated with improved PPG control from 12.6 mmol/l to approximately 9 mmol/l (PPG data for the six-month endpoint was not available) (see Table 1).

Discussion
This case highlights two important stages of treatment intensification in type 2 diabetes. The first important intensification step occurred in 2008 when dual metformin and sulphonylurea treatment was unable to maintain HbA1c targets. It is likely that the deterioration in HbA1c observed in 2008 reflected a reduction in beta-cell function, thereby requiring insulin initiation to provide an exogenous insulin source to replace the failing endogenous production.

In this case, BHI was used for insulin initiation and this provided reasonable HbA1c control between 2009 and 2010. In 2010, however, the patient’s HbA1c increased, which was associated with poor PPG control. A basal insulin would have been an alternative treatment choice for insulin initiation; however, it is likely a basal insulin would not have provided extended HbA1c control in this patient due to the need to control PPG. Thus it is likely that prandial coverage would have had to be added to the basal insulin or that the patient would have had to switch to a premix insulin regimen.

In this case, transferring the patient from BHI to BIAsp 30 improved HbA1c and PPG measurements and maintained FPG, suggesting that BIAsp 30 can offer patients important benefits over BHI. Improvements in HbA1c and PPG have been demonstrated in randomised controlled trials of BIAsp compared with BHI 30.6,7 These results are also in agreement with an analysis of almost 3,856 patients included in the IMPROVE™ observational study who switched from a premix human insulin to BIAsp 30.6 Switching from BHI to BIAsp 30 significantly improved HbA1c, FPG and PPG and significantly reduced the risk of hypoglycaemia compared with baseline treatment (p<0.0001 for all measures).12

In conclusion, switching from BHI 30 to BIAsp 30 was associated with improved glycaemic control.

Case Report 2 – Patient with Severe Nocturnal Hypoglycaemia with Biphasic Human Insulin 30
Hypoglycaemia is most common in type 1 diabetes but also affects patients with type 2 diabetes. Nocturnal hypoglycaemia in particular can cause great distress to family members who have to assist the patient, although patients themselves may be unaware of the episode.13 The following case describes a patient who experienced recurrent nocturnal hypoglycaemia with both neutral protamine Hagedorn (NPH) insulin and BHI 30, and describes the resolution of recurrent nocturnal hypoglycaemic episodes following the initiation of BIAsp 30.

Case Report
JF was a 68-year-old male patient who was diagnosed with type 2 diabetes at age 64. He had a body weight of 74 kg and a BMI of 24.9 kg/m². He had a history of hypertension and was receiving simvastatin, an angiotensin-converting enzyme (ACE) inhibitor, and thiazide.

Prior Diabetes Treatment
At diagnosis he had an HbA1c of 7.9% (63 mmol/mol) and was initiated with metformin plus a sulphonylurea. Later, he was switched to metformin plus once-daily NPH insulin, after which his HbA1c dropped to 7.0% (53 mmol/mol). This regimen was causing great distress to his wife, due to multiple episodes of severe nocturnal hypoglycaemia, of which the patient himself had no recollection. Over a period of six months he was switched from once-daily NPH to once-daily BHI 30 (Mixtard® 30/70) and then to twice-daily BHI. Over time, the patient’s BHI 30 was titrated to 32 U at breakfast and 36 U with dinner.

Table 1: Six-month Follow-up Following Initiation of Biphasic Insulin Aspart 30

<table>
<thead>
<tr>
<th>Case Parameter</th>
<th>Time after Treatment Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 Weeks</td>
</tr>
<tr>
<td>HbA1c, % (mmol/mol)</td>
<td>7.2 (55)</td>
</tr>
<tr>
<td>FPG, mmol/l</td>
<td>5.1</td>
</tr>
<tr>
<td>Self-measured PPG, mmol/l</td>
<td>9.0</td>
</tr>
<tr>
<td>Hypoglycaemic events, number</td>
<td>0</td>
</tr>
<tr>
<td>Change in body weight, kg</td>
<td>+1</td>
</tr>
</tbody>
</table>

**Figure 1: Treatment Algorithm for a 68-year-old Male Patient with Type 2 Diabetes of Four Years’ Duration**

**Prior Therapy**
- Combination OAD therapy
  - HbA1c of 7.9% (63 mmol/mol) at diagnosis
  - Initiated with metformin plus a sulphonylurea

**Initiation of basal insulin**
- Switched to metformin plus OD NPH insulin
- HbA1c dropped to 7.0% (53 mmol/mol)
- Wife distressed due to multiple episodes of severe nocturnal hypoglycaemia

**Initiation of premix human insulin**
- Over 4 months, treatment switched from OD NPH insulin to OD BHI (Mixtard® 30/70) and then to BID BHI
- Patient titrated BHI to 32 U at breakfast and 36 U with dinner
- HbA1c dropped to 7.0% (53 mmol/mol), FPG 5.5 mmol/l, PPG 9.2 mmol/l
- Nocturnal hypoglycaemia remained an issue

**Initiation of premix insulin analogue**
- BIAsp 30 initiated with 32 U at breakfast and 36 U at dinner
- 4-month follow-up
  - No severe nocturnal hypoglycaemic episodes
  - HbA1c, 7.1% (54 mmol/mol), FPG, 5.2 mmol/l, PPG, 9.1 mmol/l
- 7-month follow-up
  - No further hypoglycaemic episodes
  - HbA1c, 6.9% (52 mmol/mol), FPG, 5.0 mmol/l, PPG, 8.9 mmol/l
Figure 2: Risk of Nocturnal Hypoglycaemia

<table>
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<tr>
<th>Trial</th>
<th>Rate ratio (95% CI)</th>
<th>p</th>
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<tbody>
<tr>
<td>0.57</td>
<td>0.20–1.58</td>
<td>0.28</td>
</tr>
<tr>
<td>0.89</td>
<td>0.25–3.16</td>
<td>0.86</td>
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<tr>
<td>0.44</td>
<td>0.22–0.89</td>
<td>0.02</td>
</tr>
<tr>
<td>1.03</td>
<td>0.42–2.53</td>
<td>0.95</td>
</tr>
<tr>
<td>1.03</td>
<td>0.38–2.76</td>
<td>0.96</td>
</tr>
<tr>
<td>0.33</td>
<td>0.21–0.51</td>
<td>0.01</td>
</tr>
<tr>
<td>0.44</td>
<td>0.11–1.47</td>
<td>0.17</td>
</tr>
<tr>
<td>1.05</td>
<td>0.11–10.09</td>
<td>0.97</td>
</tr>
<tr>
<td>2.43</td>
<td>0.31–18.88</td>
<td>0.39</td>
</tr>
<tr>
<td>0.50</td>
<td>0.38–0.67</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Test of heterogeneity: F = 32 %
BHI = biphasic human insulin 30; BIAsp 30 = biphasic insulin aspart 30.

Discussion

Nocturnal hypoglycaemia can cause great distress to family members who have to assist the patient, despite the patients themselves often being unaware of the episode. In this case, the patient’s wife was very anxious due to multiple episodes of nocturnal hypoglycaemia that occurred with both basal insulin and premixed human insulin. Four months after switching treatment from BHI 30 to BIAsp 30, the patient (and his wife) reported no more severe nocturnal hypoglycaemia, and between four and seven months no further hypoglycaemic episodes were experienced. A reduction in nocturnal hypoglycaemia has been reported in a number of trials for BIAsp 30 versus BHI 30. A meta-analysis of nine BIAsp 30 trials indicated a 50 % lower rate of nocturnal hypoglycaemic episodes with BIAsp 30 versus BHI 30 (see Figure 2; p<0.01). The rate of major hypoglycaemic events was also significantly reduced by 55 % (p<0.05); however, daytime hypoglycaemia was 24 % lower for BHI 30 than for BIAsp 30 (p<0.01).

In this case, switching treatment from BHI 30 to BIAsp 30 maintained the patient’s HbA1c, FPG and PPG levels but was associated with a marked reduction in the risk of hypoglycaemic events and halted the severe nocturnal episodes that were causing great family distress.