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

Jens Sandahl Christiansen

Professor, Department of Endocrinology and Diabetes, The University of Aarhus and Consultant, Department of Medicine (Endocrinology), Aarhus University Hospital

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_{1c}) control. Case 2: switching from BHI to BIAsp 30 due to nocturnal hypoglycaemia. Case 1: HbA_{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_{1c}, insulin, postprandial glucose (PPG), type 2 diabetes

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Correspondence: Jens Sandahl Christiansen, Department of Endocrinology-M, Aarhus University Hospital, 8000 Aarhus C, Denmark. E: jsc@ki.au.dk

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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.[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.[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^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 acetylsalicyclic acid (aspirin).

Prior Diabetes Treatment

At diagnosis in 2003 he had a glycosylated haemoglobin (HbA_{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_{1c} was stable at 7.4 % (57 mmol/mol); however, an HbA_{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_{1c}, which fell to 7.2 % (55 mmol/mol) in 2009. However, in 2010 his HbA_{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_{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 HbA_{1c} 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 HbA_{1c} targets. It is likely that the deterioration in HbA_{1c} 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 HbA_{1c} control between 2009 and 2010. In 2010, however, the patient's HbA_{1c} 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 HbA_{1c} 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 be switched to a premix insulin regimen.

In this case, transferring the patient from BHI to BIAsp 30 improved HbA_{1c} and PPG measurements and maintained FPG, suggesting that BIAsp 30 can offer patients important benefits over BHI. Improvements in HbA_{1c} and PPG have been demonstrated in randomised controlled trials of BIAsp compared with BHI 30.[10,11] 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.[12] Switching from BHI to BIAsp 30 significantly improved HbA_{1c}, 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

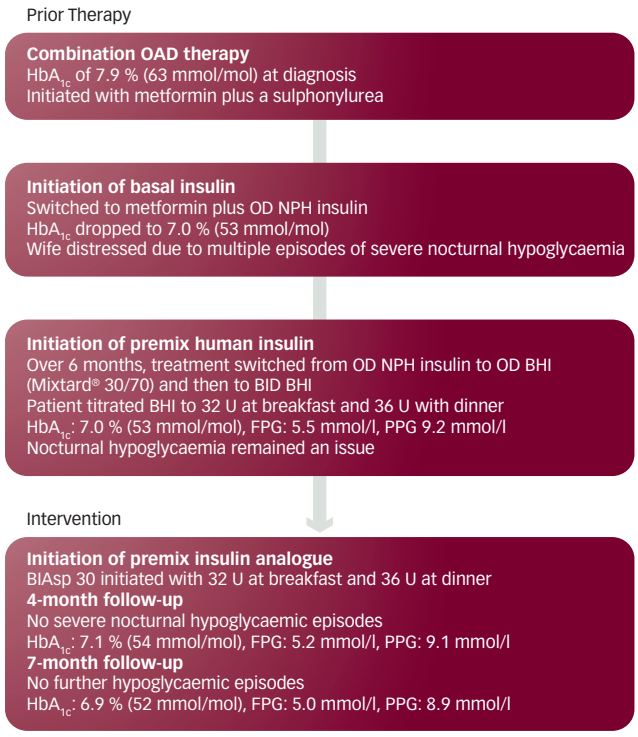
JF was a 68-year-old male patient who was diagnosed with type 2 diabetes at age 64. He had a body weight of 74 kg and a BMI of 24.9 kg/m^2. He had a history of hypertension and was receiving simvastatin, an angiotensin-converting enzyme (ACE) inhibitor, and thiazide.

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

Case Parameter	Time after Treatment Change		
	10 Weeks	19 Weeks	6 Months
HbA_{1c}, % (mmol/mol)	7.2 (55)	6.8 (51)	6.9 (52)
FPG, mmol/l	5.1	5.0	Not reported
Self-measured PPG, mmol/l	9.0	9.1	Not reported
Hypoglycaemic events, number	0	Not reported	Not reported
Change in body weight, kg	+1	Not reported	Not reported

FPG = fasting plasma glucose; PPG = postprandial glucose.

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

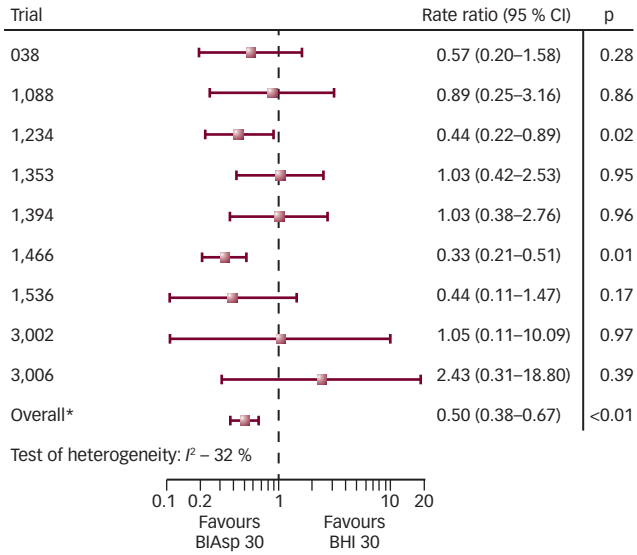


BHI = biphasic human insulin; BIAsp = biphasic insulin aspart; BID = twice daily; FPG = fasting plasma glucose; NPH = neutral protamine Hagedorn; OAD = oral anti-diabetic drug; OD = once daily; PPG = postprandial glucose.

Prior Diabetes Treatment

At diagnosis he had an HbA_{1c} 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 HbA_{1c} 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 30. Over time, the patient's BHI 30 was titrated to 32 U at breakfast and 36 U with dinner. This treatment had succeeded in maintaining his HbA_{1c} at 7.0 % (53 mmol/mol) with a mean FPG of 5.5 mmol/l and a mean PPG of 9.2 mmol/l; however, severe nocturnal hypoglycaemia remained an issue.

Figure 2: Risk of Nocturnal Hypoglycaemia



BHI = biphasic human insulin 30; BIAsp 30 = biphasic insulin aspart 30.
Figure adapted from Davidson et al, 2009. © Elsevier 2009. Reprinted with permission from Elsevier (78338). Clinical Therapeutics *2009;31:1641–51.*

Intervention

In discussing options to address the hypoglycaemia, the patient indicated that he was unwilling to reduce his evening insulin dose as he felt that this was associated with unacceptably high morning FPG values. Therefore, two further options for switching insulin were discussed with the patient: namely, switching from human premix insulin to a premixed insulin analogue or switching to a basal–bolus approach. The basal–bolus approach was rejected by the patient due to the number of daily injections required. Therefore, it was decided to initiate BIAsp 30 with a starting dose of 32 U at breakfast and 36 U at dinner. At four months, the patient reported that his wife was very satisfied with the treatment as she had not had to assist him with any severe nocturnal hypoglycaemic episodes. His HbA_{1c} was 7.1 % (54 mmol/mol) and both his FPG and PPG (5.2 mmol/l and 9.1 mmol/l, respectively) remained similar to baseline (see *Figure 1*). At seven months, the patient confirmed that he had experienced no further hypoglycaemic episodes. His glycaemic control remained stable with an HbA_{1c} of 6.9 % (52 mmol/mol), FPG of 5.0 mmol/l and PPG of 8.9 mmol/l (see *Figure 1*).

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*; $p<0.01$).[9] 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 ($p<0.01$).[9]

In this case, switching treatment from BHI 30 to BIAsp 30 maintained the patient's HbA_{1c}, 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. ■

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