Biphasic insulin aspart 30/70 (BIAsp 30): pharmacokinetics (PK) and pharmacodynamics (PD) in comparison with once-daily biphasic human insulin and basal–bolus therapy

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Objective: Pharmacological profiles of biphasic insulin aspart 30/70 (BIAsp30) once-daily (OD), twice-daily (BID) and three-times-daily (TID) were compared with other insulin regimens in two crossover glucose-clamp studies in insulin-treated type 2 diabetes patients.

Methods: Study 1: BIAsp30 OD, BID and TID vs. biphasic human insulin 30/70 (BHI30) OD (n=24). Study 2: BIAsp30 TID vs. basal–bolus (insulin glargine OD plus insulin glulisine TID) (n=24). Pharmacokinetics/pharmacodynamics (PK/PD) were investigated over 24h.

Results: Study 1: PK and PD were markedly different between BIAsp30 OD and BHI30 OD: maximum insulin concentration and glucose infusion rate (GIR) were higher for BIAsp30; time to maximum metabolism was 1.7h sooner for BIAsp30. Study 2: both regimens showed three distinct prandial-related GIR peaks. GIR 24h area-under-the-curve for BIAsp TID was higher than for basal–bolus: 2585.2 vs. 2289.2 mg/kg.

Conclusions: BIAsp had pharmacological advantages over BHI. BIAsp TID had a similar PD profile to basal–bolus.
Premixed insulin analogs are a commonly prescribed first insulin therapy for type 2 diabetes (T2D) patients, and may be a simpler alternative to basal–bolus therapy (1,2). Compared with biphasic human insulin 30/70 (BHI 30), the modern premixed insulin analog, biphasic insulin aspart 30/70 (BIAsp 30), has pharmacokinetics that more closely match endogenous insulin secretion (3,4). Therefore, an initial once-daily (OD) BIAsp 30 regimen can be safely intensified to twice-daily (BID) or three-times-daily (TID) injections (5). To compare the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of these different regimens, two crossover glucose-clamp studies were carried out in insulin-treated patients with T2D.

RESEARCH DESIGN AND METHODS

The randomized, open-label, crossover clamp studies investigated the PK/PD profiles of the following regimens:

**Study 1**: BIAsp 30 OD, BID and TID vs. BHI 30 OD

**Study 2**: BIAsp 30 TID vs. basal–bolus (insulin glargine OD plus insulin glulisine TID).

**Patients**: All participants had T2D for ≥12 months and were insulin-treated for ≥3 months with no oral therapy for ≥6 months.

**Study 1**: 31 people screened; 24 randomized (21 male, mean [SD] age 54.3 [5.5] years, BMI 32.2 [3.2] kg/m², HbA₁c 8.5 [0.9]%, insulin dose 0.7 [0.2] (range 0.3–1.1) U/kg/day). Study 2: 36 people screened; 24 randomized (21 male, mean age 52.4 [7.6] years, BMI 31.9 [4.1] kg/m², HbA₁c 8.7 [1.1]%, insulin dose 0.7 [0.1] (range 0.6–0.9) U/kg/day).

All participants gave informed consent; study procedures were carried out in accordance with the Declaration of Helsinki.

**Study designs and procedures**: **Study 1** - participants attended four separate study days (random order), 5–21 days apart, and received one, two or three injections of trial insulin at each visit: OD: 0.6 (l)U/kg of BHI 30 or BIAsp 30 administered at 19.00h; BID BIAsp 30: 0.5 U/kg at 07.00h and 0.6 U/kg 19.00h; TID BIAsp 30: 0.5 U/kg at 07.00h, 0.3 U/kg at 13.00h and 0.6 U/kg 19.00h (all supplied in 3 mL Penfill® cartridges; Novo Nordisk A/S, Denmark, administered subcutaneously).

**Study 2** - participants attended two separate study days (random order, with an injection of study drug the evening before testing), 5–21 days apart, and received injections of BIAsp 30 TID (total: 0.72±0.12 U/kg, 40% of dose at 07.00h, 20% at 13.00h, and 40% at 19.00h) or insulin glulisine (total: 0.29±0.05 U/kg, 13.3% of total dose (0.1 U/kg) each at 07.00h, 13.00h, and 19.00h) plus insulin glargine (60% of dose [0.44±0.07 U/kg] at 23.00h). Participants’ total dose was the same for each regimen.

The glucose clamp procedure was similar for both studies: at each dosing visit, patients underwent a 24h euglycemic glucose-clamp using a Biostator (glucose-controlled insulin infusion system, MTB Medizintechnik, Germany), while fasting. Blood glucose was clamped at 5.0 mmol/L by adjusting the intravenous glucose infusion. Blood samples were taken from subjects before test insulin dosing and during the glucose clamps for PK serum insulin measurements. The Biostator recorded PD glucose-infusion rates (GIR) during the clamps.

**Statistics**: Regimens were compared using 24h plots of serum
insulin (not shown for study 2) and GIR. Area-under-the-curve (AUC) measurements were taken from insulin concentration–time plots and GIR–time plots using the trapezoidal rule. Due to the different insulin doses used, statistical analyses were performed only on data from BIAsp 30 OD and BHI 30 OD (study 1, both 0.6 U/kg).

RESULTS

One participant withdrew from each study, leaving 23 completers in each.

Study 1: 24h serum insulin and GIR profiles of BHI 30 OD and BIAsp 30 OD, BID and TID showed marked differences (Figure 1a, b). Maximum serum insulin concentrations were greater for BIAsp 30 than for BHI 30 (73.1–100.4 mU/L [first injection of each regimen] vs. 46.7 mU/L, respectively). Time to maximum serum insulin concentration was shorter for BIAsp 30 than for BHI 30 (2.1–2.6h [first injection of each regimen] vs. 3.2h, respectively). The insulin AUC$_{24h}$ for BIAsp 30 OD was greater than for BHI 30 OD. The AUC$_{24h}$ for the BIAsp 30 regimens reflected total insulin dose: OD (0.6 U/kg) 668.1±191.0 mU/L·h; BID (1.1 U/kg) 1123.5±280.0 mU/L·h, TID (1.4 U/kg) 1405.0±329.7 mU/L·h.

Maximum GIR was significantly higher for BIAsp 30 OD than for BHI 30 OD (3.7 vs. 2.9 mg/kg/min; p=0.0030); time to maximum effect was 5.2 hours post-injection for BIAsp 30 OD and 5.7 hours for BHI 30 OD (p=0.0855).

Study 2: 24h GIR profiles of BIAsp TID and basal–bolus therapy (insulin glargine OD/glulisine TID) showed three distinct peaks reflecting prandial injections (Figure 1c). Maximum GIR was similar for BIAsp 30 TID and basal–bolus therapy following the first two injections, but larger for BIAsp 30 after the third: 07.00h, 2.55 vs. 2.42 mg/kg/min; 13.00h, 2.47 vs. 2.77 mg/kg/min; 19.00h, 3.52 vs. 2.70 mg/kg/min. Maximum effect was reached in slightly less time for basal–bolus therapy: 07.00h, 3.09 vs. 2.61 hours; 13.00h, 2.77 vs. 2.65 hours; 19.00h, 3.68 vs. 3.35 hours. The GIR AUC$_{24h}$ for BIAsp 30 TID was slightly higher than for basal–bolus therapy: 2585.2±1165 mg/kg vs. 2289.2±1095 mg/kg.

CONCLUSIONS

The PK and PD profiles of BHI 30 and BIAsp 30 OD, BID and TID were well characterized. BIAsp 30 OD had pharmacological advantages over BHI 30 OD (earlier and higher serum insulin levels), which may confer greater postprandial glycemic control (3, 6–8). During the 24h clamp, serum insulin following BIAsp 30 OD and BHI 30 OD returned to similar levels, suggesting that the duration of action of protaminated aspart is similar to that of NPH insulin (3,4).

BIAsp 30 TID gave a similar PD profile to that of basal–bolus therapy with insulin glargine/glulisine, and demonstrated slightly greater overall metabolic effect at the same total dose, possibly due to the higher GIR following the third daily injection. This greater glucose-lowering effect with BIAsp 30 during the evening/nighttime may pose an increased risk of nocturnal hypoglycaemia, so careful titration of the evening injection is needed. If these pharmacological results can be confirmed in a clinical trial, BIAsp 30 TID may represent an alternative to basal–bolus therapy requiring at least one fewer daily injection.

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REFERENCES
**Figure.** Pharmacokinetic and pharmacodynamic profiles following injections of test insulins in two studies in patients with type 2 diabetes, obtained using a euglycemic clamp procedure.

**a.** Study 1: 24h serum insulin profiles during which patients received BIAsp 30 either once- (19.00h), twice- (07.00 and 19.00h) or three-times-daily (07.00, 13.00 and 19.00h), or BHI 30 once-daily (19.00h). The 24h profiles have been overlain for ease of comparison.

**b.** Study 1: 24h glucose infusion rate profiles during which patients received BIAsp 30 either once- (19.00h), twice- (07.00 and 19.00h) or three-times-daily (07.00, 13.00 and 19.00h), or BHI 30 once-daily (19.00h). The 24h profiles have been overlain for ease of comparison.

**c.** Study 2: 24h glucose infusion rate profiles during which patients received BIAsp 30 three-times-daily (07.00, 13.00 and 19.00h) or basal–bolus therapy using insulin glargine once-daily (23.00h on the day before the clamp, and again on the day of the clamp) plus insulin glulisine three-times-daily (07.00, 13.00 and 19.00h).
PK/PD of BIAsp 30 regimens vs. other insulins