Biphasic Insulin Aspart 30/70: Pharmacokinetics and Pharmacodynamics Compared With Once-Daily Biphasic Human Insulin and Basal-Bolus Therapy

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OBJECTIVE — Pharmacological profiles of biphasic insulin aspart 30/70 (BIAsp 30) once daily (OD), twice daily (b.i.d.), and three times daily (t.i.d.) were compared with other insulin regimens in two crossover glucose clamp studies of insulin-treated type 2 diabetic patients.

RESEARCH DESIGNS AND METHODS — Study 1 consisted of BIAsp 30 OD, b.i.d., and t.i.d. versus biphasic human insulin 30/70 (BHI 30), OD ($n = 24$). Study 2 examined BIAsp 30 t.i.d. versus basal-bolus therapy (insulin glargine OD plus insulin glulisine t.i.d.) ($n = 24$). Pharmacokinetics/pharmacodynamics (PK/PD) were investigated over 24 h.

RESULTS — Study 1: PK and PD were markedly different between BIAsp 30 OD and BHI 30 OD: the maximum insulin concentration and glucose infusion rate (GIR) were higher for BIAsp 30; time to maximum metabolism was 1.7 h sooner for BIAsp 30. Study 2: both regimens showed three distinct prandial-related GIR peaks. GIR 24-h area under the curve for BIAsp t.i.d. was higher than for basal-bolus therapy: 2,585.2 vs. 2,289.2 mg/kg.

CONCLUSIONS — BIAsp had pharmacological advantages over BHI. BIAsp t.i.d. had a similar PD profile to basal-bolus therapy.

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Premixed insulin analogs are a commonly prescribed first insulin therapy for type 2 diabetic 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 (PK) 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 (b.i.d.) or three-times-daily (t.i.d.) injections (5). To compare the PK and pharmacodynamic (PD) profiles of these different regimens, two crossover glucose clamp studies were carried out in insulin-treated patients with type 2 diabetes.

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, b.i.d., and t.i.d. versus BHI 30 OD.
Study 2. BIAsp 30 t.i.d. versus basal-bolus therapy (insulin glargine OD plus insulin glulisine t.i.d.). All participants had type 2 diabetes for ≥12 months and were insulin treated for ≥3 months with no oral therapy for ≥6 months.

In study 1, of 31 people screened, 24 were randomized (21 men, age 54.3 ± 5.5 years, BMI 32.2 ± 3.2 kg/m^2, A1C 8.5 ± 0.9%, insulin dose 0.7 ± 0.2 [range 0.3–1.1] units · kg^{-1} · day^{-1}). In study 2, of 36 people screened, 24 were randomized (21 men, age 52.4 ± 7.6 years, BMI 31.9 ± 4.1 kg/m^2, A1C 8.7 ± 1.1%, insulin dose 0.7 ± 0.1 [range 0.6–0.9] units · kg^{-1} · day^{-1}).

All participants gave informed consent. The 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 (I)U/kg of BHI 30 or BIAsp 30 administered at 1900 h; b.i.d. BIAsp 30 0.5 units/kg at 0700 h and 0.6 units/kg at 1900 h; t.i.d. BIAsp 30 0.5 units/kg at 0700 h, 0.3 units/kg at 1300 h, and 0.6 units/kg at 1900 h. All were administered subcutaneously and supplied in 3-ml Penfill cartridges (Novo Nordisk, Denmark).

Study 2. Participants attended two separate study days (random order, with an injection of the study drug the evening before testing), 5–21 days apart. They received injections of BIAsp 30 t.i.d. (total 0.72 ± 0.12 units/kg, 40% of dose at 0700 h, 20% at 1300 h, and 40% at 1900 h) or insulin glulisine (total 0.29 ± 0.05 units/kg, 13.3% of total dose [0.1 units/kg] each at 0700 h, 1300 h, and 1900 h) plus insulin glargine (60% of dose [0.44 ± 0.07 units/kg] at 2300 h). Each participant's total dose was the same for each regimen.

The glucose clamp procedure was similar for both studies: at each dosing visit, patients underwent a 24-h euglycemic glucose clamp using a glucose-controlled insulin infusion system (Biostator; MTB Medizintechnik, Germany) while fasting. Blood glucose was clamped at 5.0 mmol/l by adjusting the intravenous glucose infusion. Blood sam-

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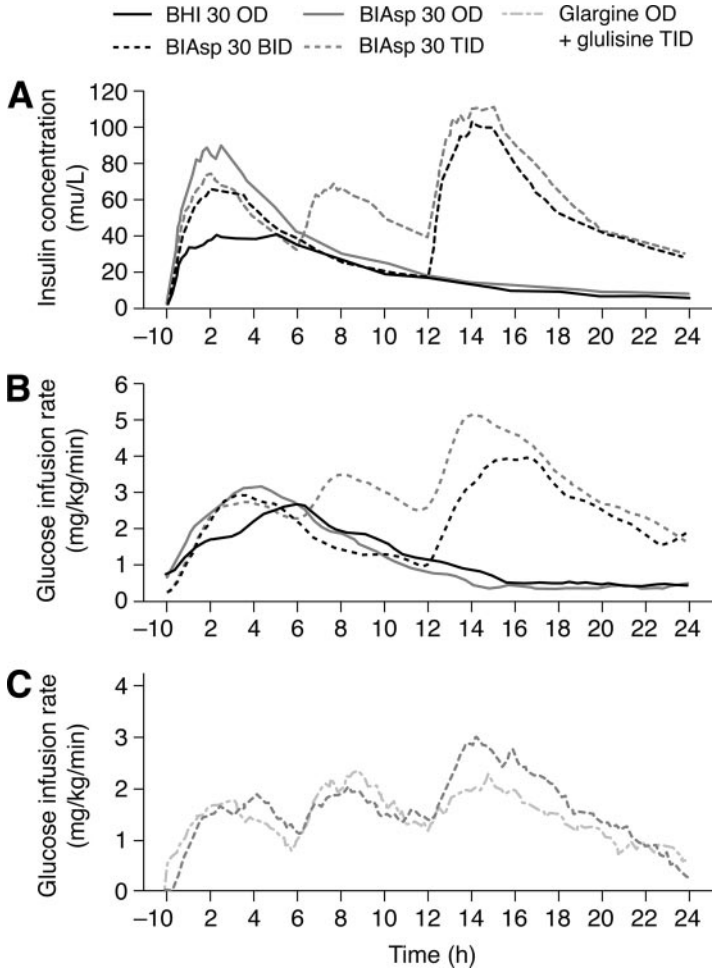

Figure 1—*PK and PD profiles following injections of test insulins in two studies in patients with type 2 diabetes, obtained using a euglycemic clamp procedure.* A*: Study 1: 24-h serum insulin profiles during which patients received BIAsp 30 once (1900 h), twice (0700 and 1900 h), or three times (0700, 1300, and 1900 h) daily, or BHI 30 once daily (1900 h). The 24-h profiles have been overlain for ease of comparison.* B*: Study 1: 24-h GIR profiles during which patients received BIAsp 30 once (1900 h), twice (0700 and 1900 h), or three times (0700, 1300, and 1900 h) daily, or BHI 30 once daily (1900 h). The 24-h profiles have been overlain for ease of comparison.* C*: Study 2: 24-h GIR profiles during which patients received BIAsp 30 three times daily (0700, 1300, and 1900 h) or basal-bolus therapy using insulin glargine once daily (2300 h on the day before the clamp and again on the day of the clamp) plus insulin glulisine three times daily (0700, 1300, and 1900 h).*

ples 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 (GIRs) during the clamps.

Statistics. Regimens were compared using 24-h 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 units/kg).

RESULTS

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

Study 1. The 24-h serum insulin and GIR profiles of BHI 30 OD and BIAsp 30 OD, b.i.d., and t.i.d. showed marked differences (Fig. 1*A* and *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 (2.1–2.6 h [first injection of each regimen] vs. 3.2 h, 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 units/kg) 668.1 ± 191.0 mU · l^{-1} · h^{-1}; b.i.d. (1.1 units/kg) 1,123.5 ± 280.0 mU · l^{-1} · h^{-1}, t.i.d. (1.4 units/kg) 1,405.0 ± 329.7 mU · l^{-1} · h^{-1}.

Maximum GIR was significantly higher for BIAsp 30 OD than for BHI 30 OD (3.7 vs. 2.9 mg · kg^{-1} · min^{-1}; P = 0.0030); time to maximum effect was 5.2 h postinjection for BIAsp 30 OD and 5.7 h for BHI 30 OD (P = 0.0855).

Study 2. The 24-h GIR profiles of BIAsp t.i.d. and basal-bolus therapy (insulin glargine OD/glulisine t.i.d.) showed three distinct peaks reflecting prandial injections (Fig. 1*C*). Maximum GIR was similar for BIAsp 30 t.i.d. and basal-bolus therapy following the first two injections but larger for BIAsp 30 after the third: 0700 h, 2.55 vs. 2.42 mg · kg^{-1} · min^{-1}; 1300 h, 2.47 vs. 2.77 mg · kg^{-1} · min^{-1}; 1900 h, 3.52 vs. 2.70 mg · kg^{-1} · min^{-1}. Maximum effect was reached in slightly less time for basal-bolus therapy: 0700 h, 3.09 vs. 2.61 h; 1300 h, 2.77 vs. 2.65 h; 1900 h, 3.68 vs. 3.35 h. The GIR AUC_{24h} for BIAsp 30 t.i.d. was slightly higher than for basal-bolus therapy: 2,585.2 ± 1,165 vs. 2,289.2 ± 1,095 mg/kg.

CONCLUSIONS

The PK and PD profiles of BHI 30 and BIAsp 30 OD, b.i.d., and t.i.d. 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 24-h 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 t.i.d. 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 hypoglycemia, so careful titration of the evening injection is needed. If these pharmacological results can be confirmed in a clinical trial, BIAsp 30 t.i.d. may represent an alternative to basal-bolus therapy requiring at least one fewer daily injection.

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