

OBSERVATIONS

Pharmacokinetics of Insulin Aspart in Pump-Treated Subjects With Type 1 Diabetes: Reproducibility and Effect of Age, Weight, and Duration of Diabetes

Insulin aspart, lispro, or glulisine are recommended in pump-treated type 1 diabetes (T1D). Aspart pharmacokinetics has been studied (1), but little is known about its reproducibility and associations with anthropometric and clinical factors.

We analyzed retrospectively data collected in 70 pump-treated subjects with T1D, comprising 39 females, 46 young, with mean (SD) BMI 22.7 (4.2) kg/m², A1C 8.1% (1.3) (65.3 [14.4] mmol/mol), and total daily insulin 0.8 (0.3) units/kg/day, who were undergoing investigations, with ethical approval, of closed-loop insulin delivery. Participants/guardians signed consent/assent as appropriate. Participants were admitted twice to the research facility, 1–6 weeks apart, for 15–37 h, and consumed 1–4 meals accompanied by prandial insulin aspart. Basal aspart

was delivered using closed-loop insulin delivery or conventional pump therapy. Venous blood samples were collected every 30–60 min to measure plasma insulin (Invitron, Monmouth, U.K.).

From 5,804 plasma insulin measurements, we estimated, using a two-compartment model, the time-to-peak plasma insulin concentration (t_{max} [min]), the metabolic clearance rate of insulin (MCR in mL/kg/min), and the background residual plasma insulin concentration (mU/L). Results are presented in Table 1. Sex differences in aspart kinetics were not observed. Aspart pharmacokinetics was weakly influenced by common clinical and anthropometric factors, because less than 20% of inter-subject variability was explained by sex, BMI, total daily dose, A1C, and diabetes duration.

We measured t_{max} comparable to literature reports (1) but observed higher inter- and intraindividual variability of t_{max} in T1D compared with healthy subjects, with intersubject coefficient of variation 33% vs. 20% and intrasubject coefficient of variation 27% vs. 15% (comparison against Heinemann et al. [2]). Nearly 40% of total variance was attributed to interoccasion variability, presumably due to variations in depth of cannula insertion, insulin site age, and local tissue perfusion. This considerable interoccasion variability suggests large inpatient variability in postprandial insulin concentration even when prandial boluses are identical. A slower insulin absorption rate was associated

with a higher BMI; the BMI z score did not alter this relationship in the young. Comparable findings using soluble insulin were reported in healthy subjects (3), but absorption of rapid-acting insulin in obese type 2 diabetes was not influenced by BMI (4).

MCR was highly reproducible. In the absence of a large bedtime bolus, overnight plasma insulin is dictated by basal pump settings. Pump settings are normally altered infrequently and, because MCR is reproducible, our data suggest that the overnight plasma insulin concentration in pump-treated patients is consistent between nights and unable to explain considerable night-to-night blood glucose variations often observed in T1D. The background insulin concentration decreased with diabetes duration. An ultrasensitive assay documented that C-peptide secretion persists over decades but decreases with disease duration (5). The background concentration observed in our data may reflect this residual secretion.

Our data lack standardization of insulin delivery, but we mitigated by the use of compartment modeling. Limitations are nonstandardized infusion sets, cannula placement, and age of cannula site likely increasing variability of absorption but representative of the standard clinical practice.

In conclusion, anthropometric and clinical factors are weakly associated with aspart pharmacokinetics. Sex does not affect aspart pharmacokinetics. The basal plasma insulin concentrations but not postprandial insulin levels are reproducible between occasions.

Table 1—Aspart pharmacokinetics, reproducibility, and correlation with clinical and anthropometric factors

| | t_{max} | MCR | I_b |
|--|-------------|------------------------------|---------------------|
| Mean (SD) or median (IQR) | 66 (22) min | 16.8 (7.4) mL/kg/min | 4.6 (1.6, 9.7) mU/L |
| Reproducibility† | SD 15 min | Coefficient of variation 15% | SD 4.7 mU/L |
| Interoccasion variation out of total variance (%) | 37 | 13 | 28 |
| Correlations | | | |
| BMI | 0.30* | 0.00 | −0.21 |
| Total daily insulin dose/kg | −0.07 | −0.06 | 0.26* |
| Age | 0.10 | 0.14 | −0.33** |
| A1C | −0.09 | 0.13 | 0.10 |
| Duration of diabetes | 0.05 | 0.31‡ | −0.38** |
| Adjusted R ² of the regression model (%)‡ | 13 | 14 | 18 |

I_b , background residual plasma insulin concentration; IQR, interquartile range. †Interoccasion variability. * $P < 0.05$. ** $P < 0.01$. ‡Model included sex, BMI, total daily dose, A1C, and duration of diabetes.

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A.H. analyzed and interpreted data and drafted, reviewed, and approved the final version of the manuscript. D.E. and M.E.W. designed studies, performed experiments, and reviewed and approved the final version of the manuscript. K.K., L.L., J.M.A., K.C., and H.R.M. performed experiments and reviewed and approved the final version of the manuscript. C.L.A., M.L.E., and D.B.D. designed studies and reviewed and approved the final version of the manuscript. M.N. analyzed data, performed experiments, and reviewed and approved the manuscript. R.H. analyzed and interpreted data, designed studies, performed experiments, and drafted, reviewed, and approved the final version of the manuscript. R.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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