

ABSTRACT

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C-peptide Correction Method to Determine Exogenous Insulin Levels in Pharmacokinetic Studies Using Technosphere® Insulin

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Background and aims: Determining the concentration time profile of exogenous-administered insulin in pharmacokinetic studies usually requires the use of patients with poor or absent β -cell function (type 1 diabetes mellitus), labeled insulin, or insulin clamp studies. These methodologies are difficult and limit the ability to explore the kinetics of novel insulins in broad populations. Although baseline C-peptide corrections have been used, they are not robust or precise.

Materials and methods: We report here the use of repeated intraindividual correlations between insulin and C-peptide to assess exogenous insulin contribution in individuals with intact β -cell function analyzed in several clinical trials (69 subjects from 3 trials). C-peptide and insulin are secreted in a 1:1 molar ratio by the pancreas, but while insulin is removed by the liver, C-peptide is not. The clearance, and ultimate ratio, differs among individuals. Data for the analysis were obtained when exogenous insulin was cleared from the plasma (ie, prior to dosing and 6 h or more after dosing with TI). The relationship was analyzed with a linear mixed effect model where the fixed effect was the population mean for intercept and slope and the random effect was the individual deviation from those means.

Results: As expected, a general linear relationship was found to exist between C-peptide and insulin, but the slope varied by individual.

$$Insulin_{i,j} = Intercept_i + Slope_i \times C-peptide_{i,j}$$

C-peptide concentrations allow the estimation of an individual's endogenous insulin concentration from the equation above. Exogenous insulin is then calculated by subtracting the endogenous insulin from the total insulin measured as per the equation below.

$$TI\ Insulin_{i,j} = Measured\ Insulin_{i,j} - Insulin_{i,j}$$

An example of the C-peptide insulin relationship is displayed in the figure on the right.

Conclusion: We suggest that this novel method may be used to replace determination of individuals' C-peptide elimination experimentally.

