Modeling Pharmacokinetic Profiles of Insulin Regimens to Enhance Understanding of Subcutaneous Insulin Regimens

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Abstract
Insulin pharmacokinetics following subcutaneous administration were modeled, simulated, and displayed through an interactive and user-friendly interface to illustrate the time course of administered insulins frequently prescribed, providing a simple tool for clinicians through a straightforward visualization of insulin regimens. Pharmacokinetic data of insulin formulations with different onset and duration of action from several clinical studies, including insulin glargine, regular insulin, neutral protamine Hagedorn (NPH), insulin lispro, and premixed preparations of NPH with regular insulin (Mix 70/30), and insulin lispro protamine suspension with insulin lispro (Mix 50/50, Mix 75/25), were used to develop a predictive population pharmacokinetic model of insulins with consideration of factors such as insulin formulation, weight-based dosing, body-weight effect on volume of distribution, and administration time relative to meals, on the insulin time-action profile. The model-predicted insulin profile of each insulin was validated and confirmed to be comparable to observed data via an external validation method. Model-based simulations of clinically relevant insulin-dosing scenarios to cater to specific initial patient and prescribing conditions were then implemented with differential equations using the R statistical program (version 3.2.2). The R package Shiny was subsequently applied to build a web browser interface to execute and visualize the model simulation outputs. The application of insulin pharmacokinetic modeling enabled informative visualization of insulin time-action profiles and provided an efficient and intuitive educational tool to quickly convey and interactively explore many insulin time-action profiles to ease the understanding of insulin formulations in clinical practice.

Keywords
insulin, pharmacokinetics, diabetes, modeling, simulation, Shiny

An estimated 415 million people worldwide are currently living with diabetes; by 2040, that number is expected to increase to 642 million.¹ Insulin replacement has been a crucial treatment for people with type 1 diabetes mellitus (T1DM) and an important adjunctive pharmacotherapy option for people with type 2 diabetes mellitus (T2DM).²,³

To optimize blood glucose control and minimize adverse outcomes, namely hypoglycemia, there is a need for adequate exogenous administration of insulin to mimic as closely as possible the pattern of physiological insulin secretion that normally occurs in healthy individuals without diabetes. To mimic the secretion and behavior of endogenous insulin and to reach optimal therapeutic effectiveness, exogenously administered insulin should ideally achieve higher insulin concentration when blood glucose is elevated at mealtimes (ie, covering postprandial needs) and lower insulin concentration between meals and during nighttime (ie, covering basal needs).⁴ To achieve this pattern of insulin secretion, an intermediate- or long-acting insulin with duration of activity that lasts at least 10 to 24 hours is often prescribed for basal insulin requirements and is commonly used in combination with a rapid-onset, short-acting insulin that has duration of activity ranging from 2 to 5 hours to cover the prandial period. Commercially available insulin products can be administered in combination, allowing appropriate flexibility in scheduling dosing times (eg, long- or intermediate-acting insulin taken at bedtime with rapid- or short-acting insulin taken prior to meals). For those patients wanting to minimize the number

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of injections, premixed formulations of insulin are also available that combine long- or intermediate- and rapid-acting insulin formulations to be delivered as a single injection.\(^5\)

Hence, it may be highly helpful to prescribers to be able to visualize the predicted time course of insulin concentration profiles when prescribing insulin therapy, as the shape of the insulin concentration-time profile directly mimics that of a glucose infusion rate-time profile from typical glucose clamp studies and also predicts the resulting glucose-time profiles.\(^6\) A visualization tool depicting snapshots of estimated insulin profiles becomes even more important for complicated situations in which the impact of several factors together, such as changing the timing or frequency of administration in a multiple-dosing regimen over the course of a day, administration of more than 1 insulin formulation, or dosing based on an individual’s body weight, can affect a patient’s overall glycemic control.

The first objective was to utilize model-based pharmacokinetic (PK) analysis to describe typical profiles of different insulins. The second objective was to leverage contemporary visualization tools to enable prescribers to see pictorial illustrations of some commonly prescribed regimens of long-acting (glargine), intermediate-acting (neutral protamine Hagedorn [NPH] or isophane), and short-acting (regular) or rapid-acting (lispro) insulins. Illustrations of premixed insulin preparations such as human insulin Mix 70/30 (70% human insulin isophane suspension + 30% human regular insulin), insulin lispro Mix 50/50 (50% insulin lispro protamine suspension + 50% insulin lispro), and insulin lispro Mix 75/25 (75% insulin lispro protamine suspension + 25% insulin lispro) are included. Some long- and rapid-acting insulin combinations, such as basal-bolus of glargine with lispro regimens, are included in the illustrations as well.

Methods
Clinical Studies
Data from 16 clinical studies were used in the analysis (Table 1). Studies were conducted according to the Declaration of Helsinki, and all subjects provided written informed consent. The studies were PK and euglycemic clamp studies and largely enrolled healthy subjects without diabetes. The insulin formulations investigated in the studies were human regular U-100 insulin (100 U/mL, U-100R, Humulin\textsuperscript{®} R U-100), human regular U-500 insulin (500 U/mL, U-500R, Humulin\textsuperscript{®} R U-500), human insulin isophane suspension (100 U/mL, NPH, Humulin\textsuperscript{®} N U-100), premixed human insulin isophane suspension and human regular insulin (100 U/mL, Mix 70/30, Humulin\textsuperscript{®} 70/30 U-100), insulin lispro (100 U/mL, IL100, Humalog\textsuperscript{®} U-100), premixed insulin lispro protamine suspension and lispro insulin (100 U/mL, Mix 50/50, Humalog\textsuperscript{®} 50/50 U-100), premixed insulin lispro protamine suspension and lispro insulin (100 U/mL, Mix 75/25, Humalog\textsuperscript{®} 75/25 U-100), insulin lispro (200 U/mL, IL200, Humalog\textsuperscript{®} U-200), and insulin glargine (100 U/mL, glargine, Basaglar\textsuperscript{®}).

Subjects were administered a single dose of insulin at each occasion, and if a study involved more than 1 administration (ie, a crossover study design), an adequate duration in the form of a washout period was ensured between doses to preclude carryover concentration effects between study periods for the exogenous insulin(s). A new baseline was established for each study period. Blood samples for the determination of serum immunoreactive insulin concentrations were collected frequently at specified intervals throughout each study. Total (bound and unbound) insulin concentrations were determined by validated radioimmunoassays that were commercially available at the time of each study conduct. Some insulins may be measured by compound-specific assay methods, so for graphical purposes of illustrating the insulins under a single unit of measure, all insulins were illustrated as regular insulin concentrations (100 U/mL). A conversion factor of 1 was applied between insulin measurements to achieve this common concentration expression if a compound-specific assay, such as for insulin glargine and insulin lispro, was utilized. The discussion of the relationship between total insulin- and insulin-lispro specific assays has been previously published.\(^7\)

Pharmacokinetic Analysis and Model Simulation
The PK data from clinical pharmacology studies were combined to provide a single data set that would allow characterization of the PK of each insulin product. Insulin concentrations and sampling times were fitted with the first-order conditional estimation with interaction method using a population PK approach implemented in a nonlinear mixed effects modeling program (NONMEM Version 7.3, ICON Development Solutions, Ellicott City, Maryland).\(^8\) Molar units were used for insulin dose and concentrations in the PK analysis and for determination of dose in the premixed insulin products. Model outputs were expressed in units (U) of regular insulin concentration, as this is more commonly used for insulin prescription in clinical practice. The dose contributed by each insulin component in the premixed product was calculated by using its respective percentage in the mixture. For example, a 10 U dose of Mix 70/30 was considered to contain 7 U of NPH and 3 U of regular insulin based on the ratios of 70% NPH to 30% regular insulin.

The model structure was based on the assumption that the absorption behavior differs among the different formulations of the same insulin type, but once
absorbed, the distribution and elimination behaviors would be the same for the same type of insulin. Hence, the insulin PK would be best described by a PK model that was parameterized by a distinct absorption rate constant (\(K_a\)) for each formulation of an insulin type, an apparent volume of distribution (\(V_d/F\)), and apparent clearance (\(CL/F\)) for each insulin type (Figure 1). The influence of body weight on insulin PK was explored as a covariate together with other patient-factor data commonly collected across insulin studies such as dose, body mass index, sex, and age. A covariate is considered to be statistically significant if it causes a reduction in model objective function value of \(\geq 6.635\) points, representing an improvement in model fit based on a 2LogLikelihood scale at a significance level of \(P < 0.01\) (degree of freedom = 1).

A baseline C-peptide correction (Equation 1) \(^9\) was applied to all insulin glargine concentrations utilized for population PK analysis to remove the impact of endogenous insulin and reflect insulin concentrations as exogenously administered insulin glargine.

\[
\text{[insulin glargine]} = \frac{[\text{immunoreactive insulin glargine}]}{[\text{Cpeptide}]} - F
\]

(1)

in which \(F\) is the average of the ratios of immunoreactive insulin glargine to C-peptide at baseline.

For regular and NPH insulins, the contribution of endogenous insulin to the insulin-sampling measurements was accounted for in the model through estimation of a baseline insulin value at time 0, prior to exogenous insulin administration. Between-subject variability of the parameter estimates was assumed to have a log-normal distribution, and a proportional error model was used for the estimation of residual variability (within subject variability and sampling error variability).

The robustness and goodness of fit of the model were evaluated separately for each insulin by a visual predictive check, conducted by simulating 200 patient replicates of each insulin using the model-estimated PK parameters. The predicted concentration-time profile of each insulin type was then overlaid on the observed concentration-time profile from a trial not used for model building in the form of an external validation procedure. For model validation of those formulations approved based on achieving bioequivalence to the reference product, such as the double-concentrated new formulation of insulin lispro 200 U/mL (Humalog\textsuperscript{⃝} U-200) and insulin glargine (Basaglar\textsuperscript{⃝}), the PK from 1 formulation (Humalog\textsuperscript{⃝} U-100 or Basaglar\textsuperscript{⃝}) was used to build the PK model, and the model predictions were then validated against the observed profiles of the other product, which are Humalog\textsuperscript{⃝} U-200 or Lantus\textsuperscript{⃝}, respectively. Because the insulin PK data were derived from healthy volunteer studies, a further validation step was conducted to confirm the robustness of the population PK model in predicting insulin PK in diabetic patients or obese populations. The predicted concentration-time curve of each insulin type should resemble that of its respective observed profile in T1DM or T2DM patients. Only when the model is verified to adequately describe the behavior of insulins would it be used for subsequent simulations of insulin concentration-over-time profiles. Simulations were implemented with differential equations using the R statistical program (version 3.2.2). Subsequently, a dashboard-like user interface that enables interactive user control for input of initial conditions and subsequent visualization of the simulation outputs was implemented via the R web browser toolkit package Shiny.\(^{10,11}\)

**Results**

**Pharmacokinetic Model**

A 1-compartment model with first-order absorption and elimination rate constants adequately described the
PK behavior of subcutaneously administered insulins. In general, the model estimated distinct absorption rate constants for each insulin type, but a common $V_{d,F}$ and $CL/F$ may be shared between some insulins, as illustrated in Figure 1. Due to the relatively flat profile for insulin glargine, both 0- ($k_0$) and first-order absorption rate constants have to be applied to adequately describe this absorption phenomenon. Similarly, the rapid onset of insulin lispro’s activity was best described by adding a 0-order absorption model on top of its first-order absorption model.

In order to mimic real-world clinical conditions, patient demographics commonly recorded across clinical trials and readily available to the clinician at the point of prescribing were considered as potential covariates to be tested for their influence on the PK of insulins. Finally, age, weight, sex, body mass index, and dose were tested as covariates on the population PK parameters. Body weight was found to exert a significant covariate impact on volume of distribution for regular insulin, insulin lispro, and insulin glargine, and on baseline endogenous insulin concentration for regular and NPH insulins, and dose was found to have a significant effect on the bioavailability parameter for insulin glargine, absorption rate constant of regular insulin, and on clearance for regular insulin. Only body weight and dose were retained as covariates in the final model. In general, both $CL/F$ and $V_{d,F}$ increased along with increasing body weight. Only covariates found to be statistically significant were retained in the final PK model, and final estimates of the population PK parameters for the insulins are listed in Table 2. Where interindividual variabilities in PK parameters can be estimated, they were generally moderate (<60%) for baseline endogenous insulin concentration, clearance, volume of distribution, and absorption rate constants, with the exception of the larger interindividual variabilities estimated at 82.4% and 74.1% for the volume of distribution of regular insulin and insulin lispro absorption rate constant.

Model Validation
The visual predictive checks indicated that the PK model described the time course and range of insulin concentrations well across the various types of insulins, as the PK observations are generally within the 90% prediction intervals from the model. In general, model medians and 90% intervals are much better aligned between predicted and observed concentrations during the time intervals where there are more observed insulin PK concentration data points (Figure 2).

Overall, the behavior of the insulin profiles are in agreement with published data in terms of time to peak concentrations and overall duration of exposures for insulin lispro 100 U/mL, human regular insulin 100 U/mL, human regular insulin 500 U/mL, insulin mixes, and NPH (Figure 2). Similarly, model-simulated profiles of insulin lispro 200 U/mL and insulin glargine (Lantus®) predicted from insulin lispro 100 U/mL and Basaglar® were confirmed to be comparable with their respective observed time-action profiles (Figure 3).

In general, the population PK model from healthy subjects predicted the profile that resembled the overall shape of the observed data in obese nondiabetic subjects given 0.25 U/kg of insulin lispro 100 U/mL (Figure 3A). Because insulin lispro 200 U/mL was found to be bioequivalent to the 100 U/mL formulation, it would have been reasonable to assume that the PK model for 100 U/mL would be able to predict the PK behavior of 200 U/mL. A confirmation of this assumption was conducted via an external validation step, utilizing data not previously used to build the insulin lispro population PK model. The model vs observation fits are as shown in Figure 3B, where the PK parameters from insulin lispro 100 U/mL in healthy subjects were found...
Table 2. Pharmacokinetic Parameter Estimates for Various Insulin Formulations

| Parameter (Unit)                          | Insulin Glargine | Regular Insulin U100 | Regular Insulin U500 | NPH Insulin | Insulin Lispro | Lispro Protamine Suspension |
|------------------------------------------|------------------|----------------------|----------------------|-------------|----------------|-----------------------------|
| Bioavailability                          |                  |                      |                      |             |                |                             |
| Bioavailability, FGlar                   | 1 (Fixed)        | –                    | –                    | –           | –              | –                           |
| Covariate effect of dose on bioavailability, \( \theta \) | –0.300 (21.4)    | –                    | –                    | –           | –              | –                           |
| Absorption                               |                  |                      |                      |             |                |                             |
| Absorption rate constant, \( K_a \) (1/h) | 0.0830 (4.25)    | 0.67 (11.1)          | 0.185 (9.08)         | 0.129 (14.3)| 0.989 (14.9)   | 0.0365 (16.5)               |
| Absorption lag, ALag (h)                 | –                | –                    | –                    | –           | 0.378 (28.0)   | –                           |
| Fraction of dose undergoing first-order absorption | 0.822 (0.00000145) | –                    | –                    | –           | 0.729 (8.49)   | –                           |
| Duration of 0-order absorption (h)       | 0.612 (4.53)     | –                    | –                    | –           | 1.06 (0.206)   | –                           |
| Covariate effect of dose on absorption rate constant | –               | –0.275 (24.9)        | –                    | –           | –              | –                           |
| Apparent volume of distribution          |                  |                      |                      |             |                |                             |
| Apparent volume of distribution (L)      | 768 (4.41)       | 178 (15.9)           | 178 (15.9)           | 178 (15.9)  | 43.0 (14.8)    | 43.0 (14.8)                |
| Covariate effect of body weight on volume of distribution | 0.00728 (32.4)   | 1.62 (27.0)          | –                    | –           | 2.48 (19.8)    | 2.48 (19.8)                |
| Apparent clearance                       |                  |                      |                      |             |                |                             |
| Apparent clearance (L/h)                 | 74.5 (2.47)      | 127 (6.36)           | 127 (6.36)           | 127 (6.36)  | 30.5 (4.49)    | 30.5 (4.49)                |
| Covariate effect of dose on clearance    | –                | –0.282 (13.6)        | –0.282 (13.6)        | –0.282 (13.6)| –              | –                           |
| Covariances                              |                  |                      |                      |             |                |                             |
| Clearance and volume of distribution     | 0.0885 (17.2)    | –                    | –                    | –           | –              | –                           |
| Clearance and absorption rate constant   | –0.0232 (28.1)   | –                    | –                    | –           | –              | –                           |
| Baseline endogenous insulin             |                  |                      |                      |             |                |                             |
| Baseline endogenous insulin concentration (pmol/L) | 79.7 (4.78)     | –                    | –                    | –           | –              | –                           |
| Covariate of body weight on baseline endogenous insulin | 0.739 (35.3)    | 0.739 (35.3)         | 0.739 (35.3)         | 0.739 (35.3)| 0.739 (35.3)   | 0.739 (35.3)               |
| Residual error                           |                  |                      |                      |             |                |                             |
| Proportional (%)                        | 31.4 (5.37)      | 29.8 (5.51)          | 29.8 (5.51)          | 29.8 (5.51) | 29.8 (5.51)    | 29.8 (5.51)                |

CV indicates coefficient of variation; Lispro, insulin lispro; Mix 70/30, premixed 70% isophane insulin suspension and 30% human regular insulin; Mix 50/50, premixed 30% insulin lispro protamine suspension and 50% insulin lispro; Mix 75/25, premixed 75% insulin lispro protamine suspension and 25% insulin lispro; NPH, neutral protamine Hagedorn; Regular U100, human regular insulin 100 U/mL; Regular U500, human regular insulin 500 U/mL; SEE, relative standard error of estimate.

to have predicted the time-action profile of insulin lispro 200 U/mL well. In addition, to ensure that the robustness of this PK model, which is largely established based on healthy volunteer data, can be extrapolated to illustrate PK profiles of the diabetic patients, the model was subsequently validated for its ability to predict insulin profiles in T1DM patients and also T2DM patients. This external validation step was conducted by overlaying typical predicted insulin concentration profiles following insulin lispro or regular insulin administration on the mean insulin concentration-time curves observed in actual clinical studies (Figures 3C to 3G). In general, the model predicted the insulin concentration-time course for individuals with diabetes relatively well using PK parameters derived from non-diabetic healthy volunteer studies.

In the final step, the model codes were translated to R to enable simulations of time-action profiles from the model. A representative median profile from each simulation was then plotted for illustrative purposes. A user-friendly web browser implemented through the R package, Shiny, allowed users to select initial dosing conditions in the form of sliding bars or drop-down menus for simulations that illustrate the concentration-time profiles of insulins in a qualitative manner that best depicts the clinical scenarios of concern. An example of the Shiny user interface is shown in Figure 4. These initial conditions include selecting the insulin formulation(s), dose, frequency of dosing, injection schedule, time of meals, number of doses, body weight, and observation duration to be displayed.

Model Utility: Illustrations of Median Insulin Concentration-Time Profiles for Specific Clinical Scenarios Following Insulin Dose Adjustments. Visual illustrations of the
representative median insulin concentration-time profiles for several commonly encountered insulin use scenarios, implemented through the Shiny package, are displayed to promote the understanding of resulting time-action profiles of insulin following subcutaneous insulin regimen adjustments tailored to meet the needs of different patients. Three common clinical scenarios are shown here as illustrative examples.

Scenario 1: Does Weight-Based Dosing of Insulin Offset the Body Weight Effect? The simulated insulin profiles based on weight-based dosing regimens of premixed insulin lispro 75/25 given twice daily at 0.5 U/kg (total) and 0.3 U/kg (total) for a 65-kg patient and an 80-kg patient are illustrated in Figure 5. Because different actual amounts of insulin were being administered to the patient of weight 65 kg vs the diabetes patient of 80 kg, the resulting insulin profiles showed that the overall shape of the profiles are comparable, and onset of the peak insulin concentrations tends to occur at approximately the same times, but actual peak concentrations between patients of different body weights tend to differ slightly despite the adoption of a weight-based dosing approach.

Scenario 2: What Do the Insulin Profiles Look Like for Commonly Prescribed Insulin Regimens? Doses were given of (A) basal insulin once daily (insulin glargine) given alone at dinner time; (B) basal insulin (insulin glargine once daily at dinner time) and a single dose of prandial insulin given at the main meal (insulin lispro at lunchtime); (C) basal insulin (insulin glargine once daily at dinner time) with prandial insulin (insulin lispro 3 times daily at meal times); (D) a premixed formulation at mealtimes (mix 50/50 3 times daily); and (E) a combination of NPH twice daily with short-acting insulin (regular insulin 3 times daily at mealtimes).

Based on the different insulin peak concentrations derived from each insulin combination, an appropriate insulin regimen can be selected according to a patient’s dietary content and meal timings. Five commonly prescribed insulin regimens are depicted in Figure 6. In Figure 6A, a basal insulin (insulin glargine) alone is used for a patient with relatively balanced insulin requirement throughout the day. However, some patients may require combined regimens, such as a basal insulin around dinner with a single rapid-acting postprandial insulin dose at the main meal of the day such as lunch.
Figure 3. External validation of the population pharmacokinetic model built on pharmacokinetic data from healthy subjects. A: Model-predicted data compared to external study with obese non-diabetic subjects given a single dose of 0.25 U/kg lispro. B: Model-predicted data compared to external study with healthy subjects given 0.3 U/kg lispro 100 U/mL or lispro 200 U/mL. C: Model-predicted data compared to external study with subjects with T1DM given 0.1 U/kg lispro TID and 0.4 U/kg NPH. D: Model-predicted data compared to external study with subjects with T2DM given 0.1 U/kg lispro. E: Model-predicted data compared to external study with T1DM given 0.15 U/kg regular TID and 0.4 U/kg NPH. F: Model-predicted data compared to external study with T1DM given 0.15 U/kg regular TID and 0.4 U/kg NPH. G: Model-predicted data compared to external study with T1DM given 0.5 U/kg glargine up to steady state (Lilly study: I2R-MC-BIAW21).

(Figure 6B) or a basal insulin with postprandial insulin doses at all 3 meals (breakfast, lunch, and dinner) (Figure 6C). Although an example of a heavy lunch meal reflecting the eating habits in some European countries is used for illustrative purposes, the model is also capable of simulating the insulin-time profile for basal insulin with a postprandial insulin regimen at dinner, which mimics more closely North American eating habits of dinner being the heaviest meal of the day. Alternatively, the insulin profile for the same dose of a premixed formulation given 3 times daily, as illustrated in Figure 6D, would be suitable for a patient who has a balanced postmeal insulin requirement. For a patient who has higher requirements for insulin in the morning, a combination of a fixed dose of short-acting regular insulin at each meal together with the option
Figure 4. Web interface to simulate pharmacokinetic profiles of insulin lispro mix 75/25 and its individual component insulins with options to depict varying initial dosing conditions.

to adjust to a higher intermediate-acting insulin dose at breakfast and a lower dose at dinner, using NPH insulin may be a more appropriate option than a premixed formulation (Figure 6E).

Scenario 3: During the Month of Ramadan, What Do the Insulin Profiles Look Like If the Lunchtime Insulin Dose Is Missed? During the month of Ramadan, Muslims who fast must abstain from eating and drinking from predawn to after sunset. Hence, diabetes patients would also alter their eating patterns to 2 meals a day at predawn and after sunset, thus skipping the lunch meal. Because of their chronic metabolic disorder, coupled with a change in dietary habit and timing of meals, insulin regimens for diabetic patients have to be adjusted accordingly during Ramadan to maintain glycemic control and at the same time minimize the risk of hypoglycemia. Figure 7 compares the insulin profiles of premixed insulin 75/25 administered 3 times daily at meal times, which depicts a typical regimen (Figure 7A), with that of various regimens modified in dose to accommodate skipping of the lunch meal during the month of Ramadan (Figures 7B and 7C), including that of a combination regimen with a higher premixed insulin content of insulin lispro 50/50 (Figure 7D) around dinnertime to cater to those patients who consume a heavy meal after breaking fast.

Discussion

Differences in onset of insulin PK profile across different insulins were accounted for through varying the absorption mechanism or disposition of each insulin in the population PK model. Because the initial tissue distributions of insulins occur more rapidly (in minutes) than their prolonged subcutaneous absorption phase, it was not possible to distinguish between these processes through PK modeling, as the process occurs far more rapidly than the time intervals between PK blood samples. Therefore, a 1-compartment model was found to adequately describe the overall PK behavior of insulin, and this is consistent with previous findings.

Because insulin doses are often prescribed in units per kilogram, body weight has a direct impact on the actual administered dose, and therefore, it is not unexpected that body weight was found to be a significant covariate in the overall population PK model across all insulin types. Given that insulin is essentially peptides, its volume of distribution is largely confined to extracellular space, which in turn is expected to
be correlated to body size. Therefore, having a weight component included in the model gives the prescribers a means of comparing the anticipated effect of a body weight–adjusted dose on the insulin time-action profile based on the absolute units of insulin administered. This may be of particular interest, for example, in the Asian or Middle-Eastern regions where insulins may be administered to diabetic patients of lower body weight, compared to the typical Western T1DM or T2DM,26 where most clinical trials leading to dose recommendations in drug labels would have been conducted. Nevertheless, it should be highlighted that the true effect of this weight covariate is confounded by weight-based dosing (U/kg) in clinical practice. Therefore, it is not possible to discern whether a weight-based dosing effect or that of body weight truly affected insulin disposition, as a body weight–based dosing regimen may at times contribute to reducing interindividual variability in PK as well as its pharmacodynamic effect.27 Simulated insulin time-action profiles confirmed that the shape and peak insulin concentrations achieved by a typical 65-kg patient and that from an 80-kg patient, when administered the same U/kg dose, were largely very similar.

Although the population model accounts for sources of variability, the main purpose of a visualization tool was to enable a quick illustration of the potential impact of a change in insulin dose, regimen, administration time, or a combination of these on the overall insulin profile. To enable the visualization of the combined effects of different insulin formulations as a single insulin-time action profile, all insulin concentrations were converted a common measure of regular insulin concentration. In the general physiology of glucose homeostasis, insulin concentrations over time (PK) profiles are considered to mimic closely their own glycodynamic time-action profile, with perhaps with only a small temporal lag in the glycodynamics.28 Hence, the PK time-action profile displayed by Shiny is a representative median insulin profile for a given set of initial conditions and insulin regimen to enable better qualitative assessment of the resulting insulin concentration–time relationship under the specific conditions and is not meant to be a tool to display the individualized time-action profile for any specific patient. In addition, its utility can be expanded to include illustrations of insulin time-action profiles in the event of a missed dose or an accidental double dose or to compare onset time, peak effect, and duration of activity when switching from 1 insulin regimen or formulation to another.

One limitation of the current model is that it incorporates only PK information and therefore cannot account for dietary modifications such as proportion of carbohydrates and meal or caloric content.
Figure 6. Simulated insulin concentration over time profiles for some commonly prescribed insulin regimens: basal insulin alone (A); basal insulin with single prandial insulin (insulin glargine with lispro at lunch) (B); basal insulin with mealtime lispro (insulin glargine with lispro 3 times daily) (C); a premixed formulation of 50/50 3 times daily at meal times (D); isophane insulin with mealtime regular insulin (NPH with regular insulin 3 times daily) (E).

This would require an extension of the current PK model to integrate insulin profiles with their consequential effects on glucose disposition. An integrated PK-pharmacodynamic model would also be necessary to discern any subtle differences in glucose response between T1DM and T2DM patients given the same insulin formulation(s). In addition, the effect of antibody formation following chronic insulin administration is out of our scope and could not be assessed, as immunogenicity information was generally lacking in insulin clamp studies where PK assessment conducted in these trials tend to be of shorter duration and assessed only insulin regimens or doses found to be safe and effective from long-term safety and efficacy trials. However, antibody formation following insulin administration such as insulin glargine has been found to be low or generally showed a lack of impact on safety and efficacy outcomes. Although the development of antibodies has been observed with the use of insulin lispro, the clinical consequences of these antibodies have been negligible in clinical practice for more than 2 decades of clinical use, and the impact of immunogenicity was found to be comparable across different formulations of rapid-acting insulins.

Conclusions
This article extends the usefulness of population PK analysis to bedside clinical practice through the ability to visualize the various PK profiles of insulins and their use in combination. This should enhance education on how insulin therapy patterns frequently used in clinical practice may be tailored to meet the needs of patients from many global regions. Model simulations
Figure 7. Simulated typical profile of premixed insulin (lispro 75/25) given at meal times (A) versus insulin profiles following different scenarios of dosing regimen adjustments during the month of Ramadan such as skipping lunch dose with lower premixed insulin dose at breakfast followed by a higher premixed dose at dinner (B); skipping lunch dose with slightly lower dose at breakfast and the usual dose at dinner (C); and skipping lunch dose with slightly lower dose at breakfast and a premixed formulation with higher lispro ratio at dinner time to cater to heavier meal after breaking fast (D).

...can now be implemented through new user-friendly software applications. The informative visualization of the concentration-time profiles of multiple insulin formulations via a customized web browser interface can also provide an easy-to-use and efficient educational tool to prescribers for conveying and interactively exploring many insulin time-action profiles in real time during the prescription of insulins in a clinical setting.

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References
1. International Diabetes Federation. Diabetes Atlas. 7th ed. http://www.diabetesatlas.org/resources/2015-atlas.html. Accessed April 21, 2016.
2. Esposito K, Capuano A, Guigliano D. Humalog (lispro) for type 2 diabetes. Expert Opin Biol Ther. 2012;12(11):1541–1550.
3. Henske JA, Griffith ML, Fowler MJ. Initiating and titration insulin in patients with type 2 diabetes. Clin Diabetes. 2009;27(2):72–76.
4. Guigliano D, Chiodini P, Maiorino MI, Bellastella G, Esposito K. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Endocrine. 2016;51(3):417–428.
5. Home PD. Plasma insulin profiles after subcutaneous injection: how close can we get to physiology in people with diabetes? Diabetes Obes Metab. 2015;17(11):1011–1020.
6. Bolli GB. The pharmacokinetic basis of insulin therapy in diabetes mellitus. Diabetes Res Clin Pract. 1989;6(4):S3–S16.
7. Bowsher RR, Lynch RA, Brown-Augsburger P, et al. Sensitive RIA for specific determination of insulin lispro. Clin Chem. 1999;45(1):104–110.
8. Beal S, Sheiner LB, Boeckmann A, Bauer RJ. NONMEN User’s Guide (1989-2009). Ellicott City, MD: Icon Development Solutions; 2009.
9. Owens DR. Human Insulin: Clinical Pharmacological Studies in Normal Man. Lancaster, England: MTP Press; 1986.
10. Shiny by RStudio. http://shiny.rstudio.com/. Accessed March 31, 2016.
11. Wojciechowski J, Hopkins AM, Upton RN. Interactive pharmacometric applications using R and the Shiny package. CPT Pharmacometrics Syst Pharmacol. 2015;4(3):e00021.
12. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys (B28), Pro (B29)]-human insulin. A rapidly absorbed analogue of human insulin. Diabetes. 1994;43(3):396–402.
13. de la Peña A, Riddle M, Morrow LA, et al. Pharmacokinetics and pharmacodynamics of high-dose human regular U-500...
insulin versus human regular U-100 insulin in healthy obese subjects. *Diabetes Care*. 2011;34(12):2496–2501.

14. Heise T, Weyer C, Serwas A, et al. Time-action profiles of novel premixed preparations of insulin lispro and NPL insulin. *Diabetes Care*. 1998;21(5):800–803.

15. de la Peña A, Yeo KP, Milicevic Z, et al. Evaluation of the pharmacodynamic (PD) and pharmacokinetic (PK) variability of NPL insulin relative to NPH insulin in healthy subjects with an adaptive design protocol [Poster]. *AAPS J*. 2006;8(Suppl 2):W4053.

16. de la Peña A, Yeo KP, Linnebjerg H, et al. Subcutaneous injection depth does not affect the pharmacokinetics or glucedynamics of insulin lispro in normal weight or healthy obese subjects. *J Diabetes Sci Technol*. 2015;9(4):824–830.

17. Linnebjerg H, Lam EC, Seger ME, et al. Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and the EU- and US-approved versions of Lantus insulin glargine in healthy subjects: three randomized euglycemic clamp studies. *Diabetes Care*. 2015;38(12):2226–2233.

18. Jacobs MA, Keulen ET, Kanc K, et al. Metabolic efficacy of preprandial administration of Lys(B28), Pro (B29) human insulin analog in IDDM patients. A comparison with human regular insulin during a three-meal test period. *Diabetes Care*. 1997;20(8):1279–1286.

19. Gagnon-Augier M, du Souich P, Baillargeon JP, et al. Dose-dependent delay of the hypoglycemic effect of short-acting insulin analogs in obese subjects with type 2 diabetes: a pharmacokinetic and pharmacodynamic study. *Diabetes Care*. 2010;33(12):2502–2507.

20. Heinemann L, Heise T, Wahl LC, et al. Prandial glycaemia after a carbohydrate-rich meal in type I diabetic patients: using the rapid acting insulin analogue [Lys(B28), Pro (B29)] human insulin. *Diabetic Med*. 1996;13(7):625–629.

21. Lam E, Garbyan P, Linnebjerg H, et al. Reduced intra-subject variability of basal insulin peglispro (BIL) compared to insulin glargine (GL) in patients with type 1 diabetes mellitus [abstract]. *Diabetologia*. 2015;58(Suppl 1):S1–S2.

22. Ahmedani MY, Alvi SF, Haque MS, Fawwad A, Basit A. Implementation of Ramadan-specific diabetes management recommendations: a multi-centered prospective study from Pakistan. *J Diabetes Metab Disord*. 2014;13(1):37.

23. Woodworth JR, Howey DC, Bowsher RR, et al. Comparative pharmacokinetics and glucodynamics of two human insulin mixtures: 70/30 and 50/50 insulin mixtures. *Diabetes Care*. 1994;17(5):366–371.

24. Osterberg O, Erichsen L, Ingwersen SH, Plum A, Poulsen HE, Vicini P. Pharmacokinetic and pharmacodynamic properties of insulin aspart and human insulin. *J Pharmacokinet Pharmacodyn*. 2003;30:221–235.

25. Nucci G, Cobelli C. Models of subcutaneous insulin kinetics: a critical review. *Comp Methods Programs Biomed*. 2000;62:249–257.

26. Walpole SC, Prieto-Merino D, Edwards P, Cleland J, Stevens G, Roberts I. The weight of nations: an estimation of adult human biomass. *BMCPub Health*. 2012;12:439.

27. Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. *J Clin Pharmacol*. 2012;52(1):18–28.

28. Ciofetta M, Lalli C, Del Sindaco P, et al. Contribution of postprandial versus interprandial blood glucose to HbA1c in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. *Diabetes Care*. 1999;22(5):795–800.

29. Ilag LL, Deeg MA, Costigan T, et al. Evaluation of immunogenicity of LY2963016 insulin glargine compared with Lantus insulin glargine in patients with type 1 or type 2 diabetes mellitus. *Diabetes Obes Metab*. 2016;18(2):159–168.

30. Mianowska B, Szadkowska A, Pietrzak I, et al. Immunogenicity of different brands of human insulin and rapid-acting insulin analogues in insulin-naive children with type 1 diabetes. *Pediatr Diabetes*. 2011;12(2):78–84.

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