Model-Based Evaluation of Exenatide Effects on the QT Interval in Healthy Subjects Following Continuous IV Infusion

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Abstract
Investigation of the cardiovascular proarrhythmic potential of a new chemical entity is now an integral part of drug development. Studies suggest that meals and glycemic changes can influence QT intervals, and a semimechanistic model has been developed that incorporates the effects of changes in glucose concentrations on heart rate (HR) and QT intervals. This analysis aimed to adapt the glucose-HR-QT model to incorporate the effects of exenatide, a drug that reduces postprandial increases in glucose concentrations. The final model includes stimulatory drug effects on glucose elimination and HR perturbations. The targeted and constant exenatide plasma concentrations (>200 pg/mL), via intravenous infusions at multiple dose levels, resulted in significant inhibition of glucose concentrations. The exenatide concentration associated with 50% of the stimulation of HR production was 584 pg/mL. After accounting for exenatide effects on glucose and HR, no additional drug effects were required to explain observed changes in the QT interval. Resulting glucose, HR, and QT profiles at all exenatide concentrations were adequately described. For therapeutic agents that alter glycemic conditions, particularly those that alter postprandial glucose, the QT interval cannot be directly compared to that with placebo without first accounting for confounding factors (eg, glucose) either through mathematical modeling or careful consideration of mealtime placement in the study design.

Keywords
glucose, heart rate, mathematical modeling, QT interval

The investigation of the potential for a new chemical entity to cause cardiac arrhythmias, as assessed by prolongation of the QT interval, is an integral evaluation during the drug development process.1–4 There are many factors that influence the QT interval, including age, sex, heart rate (HR), activity level, time of day, and meal consumption.5 Glucose-lowering agents are designed to target endpoints such as glucose and insulin exposure that can, in turn, affect the QT interval and complicate the design and assessment of a thorough QT (tQT) study.

Exenatide is an approved glucagon-like peptide-1 receptor agonist for the treatment of type 2 diabetes mellitus, which is available in 2 formulations for twice-daily6 (immediate release [IR]) and once-weekly (QW) administration.7 At therapeutic dose levels of the IR formulation, exenatide concentrations peak at approximately 2 hours postdose, with elimination occurring primarily by glomerular filtration and a half-life of about 2.4 hours.6 The extended-release formulation of exenatide is based on slow absorption from microspheres,7,8 and steady-state exenatide concentration is achieved 6 to 8 weeks after starting therapy. Drug concentrations remain relatively constant across the week-long dosing interval with the potential to provide continuous glycemic control. Once exenatide is released from the microspheres, its absorption, distribution, metabolism, and excretion characteristics remain the same as those of the IR formulation.8,9 The mechanisms of drug action for exenatide reflect glucagon-like peptide-1 receptor agonism, including glucose-dependent insulin secretion (first and second phase),10 reduction of food intake and slowing of gastric emptying,11 increased satiety, and glucagon suppression.6,12,13 Both exenatide formulations are associated with significant changes in fasting and postprandial glycemic responses.9,14

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Two tQT studies with exenatide have been conducted: 1 for the IR formulation and 1 during the development of the QW formulation. Both studies show that exenatide is not associated with QT interval prolongation. The International Conference on Harmonisation E14 guidelines for tQT studies state that the study should be a randomized, double-blind, placebo- and positive-controlled design for evaluating the QT interval across the range of clinical drug exposures. In addition, the tQT study design should accommodate the particular pharmacokinetic (PK) characteristics of the test compound. For the QW formulation of exenatide, steady-state drug concentrations are achieved after 7 to 8 weeks of QW administration, which is not convenient for QT evaluation studies. Thus, a pilot study was conducted so that various design features could be optimized prior to the actual tQT study. Exenatide was administered by intravenous (IV) infusion to achieve target steady-state drug concentrations (200, 300, and 500 pg/mL) over a useful timeframe. Pharmacodynamic (PD) variables such as HR and glycemic measurements (glucose and insulin) were obtained, and an evaluation was also performed to identify the most appropriate timing for meals relative to the primary QT assessment window.

Evaluation of the 24-hour baseline period from the pilot study identified a shortening of the QT interval occurring 2 to 3 hours after meal consumption. To better understand this observation, a semimechanistic model was developed that incorporated the effects of changes in glucose concentrations following a meal on HR and QT over the entire 24-hour baseline. Within this model, increases in glucose concentrations following a meal were associated with an increase in HR and a subsequent decrease in the QT interval as a result of the increased HR. An additional suppression of the QT interval following the meal remained, even after accounting for the HR effect. Model simulations showed that the magnitude of this additional suppression could be large enough to potentially result in a false-positive signal in a tQT study if not properly addressed through adequate planning of meal timing or accounting for glycemic changes within the analysis. This finding may be particularly important for agents that alter glucose homeostasis, in which the glycemic responses during the baseline and active treatment periods are no longer similar owing to the glucose-lowering drug action. The purpose of this study was to expand the glucose-HR-QT model (developed for baseline day) by incorporating the treatment effects of exenatide. The final model could be of value when considering design elements, analysis, and interpretation of tQT studies for drugs that alter glycemic response elements.

Methods

Subjects

This study was conducted in accordance with the principles described in the Declaration of Helsinki (1964) up to and including the Seoul revision. An institutional review board approved the clinical protocol, and all subjects provided written informed consent prior to participation. A total of 21 healthy subjects were enrolled in this open-label, phase 1 pilot study. Of the subjects had exenatide exposure and glycemic measurements available beyond the 24-hour baseline period.

Study Design

A flexible design was utilized in which subjects were allocated to 1 of 3 cohorts (cohort A, n = 6; cohort B, n = 6; and cohort C, n = 9) and admitted to an inpatient clinic for baseline period assessments followed by a 4-day stepped exenatide IV infusion regimen. The cohorts were conducted sequentially to allow for the evaluation of varying paradigms of stepped infusions and design elements with the goal of informing a subsequent tQT study (Figure 1). Baseline assessments began at 8 PM on day –2, with subjects undergoing 24-hour continuous electrocardiogram (ECG) monitoring and collection of PD endpoints. The infusion of exenatide commenced at 8 PM on day –1 and continued over a 4-day stepped exenatide IV infusion regimen, with rates ranging from 1.0 to 6.3 μg/h, in order to achieve average target steady-state concentrations of 200, 300, 500, and 700 pg/mL on days 1, 2, 3, and 4, respectively. The targeted supratherapeutic steady-state exenatide concentration for the tQT study was 500 pg/mL; therefore, only data from the baseline period through day 3 (500 pg/mL target) were used in this analysis.

Subjects received a standardized 2500 calorie/d diet, with breakfast at 7 AM (cohort A) or 6 AM (cohorts B and C), lunch at 2 PM (following the primary ECG assessment window), and dinner at 8 PM. The site dietitian recorded the specific macronutrient content of each meal and the percentage of the meal consumed. The amount of carbohydrates was used as a measure of the glucose dose in the analysis. Following exenatide administration, there was a general decrease in the percentage of meals consumed, with a median amount of 75% consumed at all 3 meals. Figure 1 provides a summary of the study design, food provided, and percentage of the meal consumed stratified by study day.

PK and PD Assessments. Plasma glucose, serum insulin, and exenatide plasma concentrations were assessed at 14 time points per day for each of the study
days. The baseline ECGs were extracted hourly, except
for 30-minute collection intervals around the breakfast
meal (7-9 AM), for a total of 26 HR and QT measure-
ments during the baseline period. For the remaining
days in the study, HR and QT were extracted at the
time points corresponding to the PD assessments (14
extractions per day). Figure 1 also provides a sum-
mary of the sampling strategy for the PK and PD
endpoints. All ECG measurements were performed in a
blinded fashion at a central laboratory as previously
reported, and the average HR and QT across 3 beats were used in the PD analysis.

Analytical Procedures
Plasma concentrations of exenatide were measured
using a validated enzyme-linked immunosorbent as-
say (Tandem Labs, San Diego, California). Interas-
say coefficient of variation (CV) was ≤6%. Assay
methodology for the PD endpoints was described
previously.

PK and PD Modeling
A semimechanistic PD model for glucose, HR, and
QT was previously developed for the 24-hour baseline
period in the pilot QT study. This model contains an
indirect response, with an increase in glucose concentra-
tion stimulating an increase in HR, and a simple direct
effect to describe the relationship between QT interval
and HR (Figure 2). In addition, diurnal variation was
incorporated into the HR model, allowing for daily
HR fluctuations and their subsequent effect on QT.
A further suppression of the QT interval, occurring
2 to 3 hours after meal consumption, was incorpo-
rated through the use of a single transit compartment.
Previously estimated parameter values are listed in
Supplemental Table S1.

A sequential approach was used to incorporate the
effects of exenatide into the model. First, the PK
associated with the IV infusion of exenatide was quan-
tified, and the individual Bayesian PK parameters were
held fixed. Subsequently, the influence of exenatide on
glycemic response and HR was estimated. The model
was evaluated for any remaining effects of exenatide on
QT after accounting for the known drug effects on both
HR and glucose.

The final PK/PD model is shown in Figure 2. The PK
of exenatide following IV infusion was best described
with a single compartment featuring linear (k_{el}) and
nonlinear elimination (K_m, V_{max}):

$$\frac{dA_{exen}}{dt} = K_0 - \left( k_{el} + \frac{V_{max}}{K_m + A_{exen}} \right) \cdot A_{exen}$$

with A_{exen} as the amount of drug in the compart-
ment and K_0 as the zero-order infusion rate con-
stant. Exenatide plasma concentration (C_p) is defined
as C_p = A_{exen}/V, with V as the volume of drug
distribution.
The influence of exenatide concentration in this system was quantified through the use of indirect response models. The relationship between exenatide concentration and glucose response was best described through the stimulation of the first-order elimination of glucose (k_{out, glu}) by the exenatide concentration:

\[
\frac{dGlu}{dt} = \frac{k_{a, glu}}{V_{glu}} \cdot A_{meal} + K_{in, glu} - k_{out, glu} \cdot \left( 1 + \frac{S_{max, glu}/exen \cdot C_p}{SC_{50, glu/exen} + C_p} \right) \cdot Glu
\]  

(2)

with \(k_{a, glu}\) as the first-order absorption rate constant of glucose in the gut (\(A_{meal}\)), \(V_{glu}\) as the volume of distribution of glucose, \(S_{max, glu}/exen\) as the maximal fold increase in the stimulation of glucose utilization, and \(SC_{50, glu/exen}\) as the exenatide concentration producing 50% of \(S_{max, glu}/exen\). The zero-order production rate constant of endogenous glucose (\(K_{in, glu}\)) was assumed to be the product of \(k_{out, glu}\) and the baseline glucose concentration (\(Glu_0\)).

The relationship between exenatide concentration and HR was also described with an indirect response model with a circadian input function (CIRC):

\[
\frac{dHR}{dt} = K_{in, HR} \cdot \left( 1 + CIRC \right) \cdot \left( 1 + \frac{S_{max, HR/exen} \cdot C_p}{SC_{50, HR/exen} + C_p} \right) - k_{out, HR} \cdot HR_0
\]  

(3)

\[
CIRC = AMP_1 \cos \left( \frac{2\pi (t - ph_1)}{24} \right) + AMP_2 \cos \left( \frac{2\pi (t - ph_2)}{12} \right)
\]  

(4)

with the zero-order input rate constant for HR (\(K_{in, HR}\)) stimulated by exenatide concentration, \(S_{max, HR/exen}\) as...
the maximum fold increase in the change in the input rate for HR, and SC<sub>50</sub>HR<sub>exen</sub> as the exenatide concentration producing 50% of S<sub>max</sub>HR<sub>exen</sub>. The zero-order production rate constant (K<sub>in,H</sub>) was assumed to be the product of k<sub>out,H</sub> and the baseline HR (HR<sub>0</sub>). Within the circadian function, the first and second periods are 24 and 12 hours, AMP<sub>1</sub> and AMP<sub>2</sub> are the amplitudes of the oscillatory functions, and φ<sub>1</sub> and φ<sub>2</sub> are the acrophase parameters. The initial conditions for glucose (Glu<sub>0</sub>) and HR (HR<sub>0</sub>) were set to the individual measured value at time 0 for each endpoint, and the initial conditions of the exenatide PK, meal, and transduction compartments were set to 0.

Interindividual variability was described assuming a log-normal distribution model, and residual variability was estimated separately for each PD endpoint (ie, glucose, HR, and QT) using proportional error models. All modeling and simulations were conducted using the first-order conditional method with interaction in NONMEM VI. Model adequacy was assessed by precision of the parameter estimates, graphical assessment, and evaluation of visual predictive checks. The visual predictive check was performed by evaluating the median and 90% prediction interval for 1000 simulations from the model in comparison to the observed data.

**Results**

*Exploratory Graphical Analysis*

The time-course profiles for the 3 primary PD endpoints (glucose, HR, and QT) across all 4 study days and stratified by cohort are shown in Supplemental Figure S1. The -24- to 0-hour time period reflects the baseline period, and 0 to 72 hours includes the stepped exenatide IV infusion treatment period. The entire study is characterized by substantial variability in the PD measurements. Key observations include the increase in HR due to exenatide treatment and the corresponding decrease in the QT interval. The median glucose concentrations over time for cohorts B and C combined, and stratified by day (ie, progressively increasing exenatide exposures), show a clear suppression of glucose concentrations during the treatment period relative to the placebo day (Figure 3). Suppression of glucose concentrations over time was evident by day 1 (200 pg/mL target drug concentration), along with decreases of approximately 25 mg/dL in the peak glucose concentration approximately 1 hour after breakfast. Little further suppression of glucose was apparent with increasing exenatide target concentrations (300 and 500 pg/mL) on days 2 and 3. The median HR over time, stratified by day, shows HR increasing from a median of approximately 65 beats per minute (bpm) during the baseline period to 74, 77, and 80 bpm with increasing exenatide concentrations on days 2, 3, and 4, respectively.

**PK Model**

The initial infusion regimen used in the trial for cohort A resulted in concentrations greater than originally targeted due to nonlinear PK, with geometric mean (SE) steady-state concentrations of 221 (4.83), 394 (11.5), and 834 (25.2) pg/mL for days 2, 3, and 4. Owing to greater-than-expected plasma drug concentrations, the infusion algorithm for cohorts B and C was altered to ensure achievement of target concentrations (Figure 1). The final geometric mean (SD) exenatide concentrations for cohorts B and C combined for days 2, 3, and 4 were 213 (3.28), 333 (6.09), and 549 (8.97) pg/mL. The PK of exenatide following an IV infusion was best described by a 1-compartment model with zero-order input and linear plus capacity-limited elimination (Equation 1). The estimated linear elimination rate constant (k<sub>e</sub>) was 0.424 h<sup>-1</sup> (7.57% CV). The concentration required for one-half of the maximal elimination rate (K<sub>m</sub>) was estimated to be 5.3 μg (K<sub>m</sub>/V<sub>c</sub> = 453 pg/mL), with a total clearance of approximately 8 L/h at a concentration of 200 pg/mL. All parameters were estimated with good precision (Table 1). Sample individual predictions and visual predictive checks are shown in Figure 4, with both panels suggesting that the model adequately described the disposition kinetics of exenatide following IV infusion.

**PK/PD Modeling**

The final PD model incorporates indirect response models to define the relationships between plasma exenatide concentrations and glucose utilization and HR (Figure 2). The model adequately recapitulates the glucose, HR, and QT interval profiles at the population (Figure 5) and individual (Supplemental Figure S2) levels without direct effects of exenatide on the QT interval. All parameters were well estimated (Table 1); however, the SC<sub>50</sub> parameter for the effect of exenatide on glucose utilization was fixed to 90 pg/mL obtained from initial modeling but was associated with poor precision and is in agreement with previously reported associated exenatide glycemic response. The steady-state plasma exenatide concentration on day 1 (200 pg/mL) was rapidly achieved and is well above the expected SC<sub>50</sub>. Thus, drug concentrations largely reside in the plateau or capacity-limited region of the concentration-effect curve (ie, stimulation function in Equation 2 approaches S<sub>max</sub>glucose<sub>exen</sub> with C<sub>p</sub> >> SC<sub>50</sub>glucose<sub>exen</sub>), resulting in poor precision for the estimation of the SC<sub>50</sub> parameter. In addition, allowing for separate estimates for the first-order glucose absorption rate constant from the meal (k<sub>a glu</sub>) for each
day improved the model-fitting criteria and revealed a progressive decrease in this absorption parameter as the exposure to exenatide increased over time. Simpler models with only a single shift in $k_a$ for treatment periods were evaluated but did not describe the data as well. The exenatide $SC_{50 HR/exen}$ for the stimulation of HR was greater than that for glucose and estimated at 584 pg/mL (44.3% CV) with relatively large, but well-estimated, interindividual variability of 83.4% (35.6% CV).

The primary endpoint of tQT studies, as defined in the U.S. Food and Drug Administration guidance,\textsuperscript{1} is the baseline-adjusted HR-corrected QT (mQTc). With the final model, simulations were conducted for
Figure 5. Final pharmacodynamic model internal qualification. Visual predictive checks are shown for glucose, HR, and QT. Symbols represent individual observed data, dashed lines represent the 50th percentiles of the observed data, and solid lines represent medians of the simulations. Shaded areas define the 5th to 95th percentiles of 1000 simulations. bpm, beats per minute; HR, heart rate.

Table 1. Final PK/PD Parameter Estimates for Exenatide in Healthy Volunteers

| Parameter | Parameter Estimate | %RSE | IIV(%) | %RSE |
|-----------|--------------------|------|--------|-------|
| Kel (1/h) | 0.424              | 7.57 | 17.9   | 36.2  |
| Km (μg)  | 5.3                | 29.2 | 104    | 31    |
| Vmax (μg/h)| 1.79              | 9.66 |        |       |
| V (L)     | 11.7               | 7.17 | 24.6   | 43.7  |
| cov (IIV V, IIV Km) | 0.23    | 35.8 |        |       |
| RVexen (%CV) | 9.03               | 12.3 |        |       |
| Smaxglu/exen | 0.77             | 22.7 | 93.7   | 73.1  |
| SC50glu/exen | 90                | NE   |        |       |
| k_a_glu, day 1 (1/h) | 1.72 | NE   |        |       |
| k_a_glu, day 2 (1/h) | 0.162 | 29.8 |        |       |
| k_a_glu, day 3 (1/h) | 0.121 | 41.4 |        |       |
| k_a_glu, day 4 (1/h) | 0.194 | 43.6 |        |       |
| Smaxgluisoexen | 0.527             | 23.7 |        |       |
| SC50gluisoexen (μg/mL)| 584 | 44.3 | 83.4   | 35.6  |
| RVHR     | 7.82               | 9.55 |        |       |
| RVQT     | 2.9                | 9.64 |        |       |
| RVGlu    | 10.4               | 15.7 |        |       |

cov, covariance; CV, coefficient of variation; HR, heart rate; IIV, interindividual variability; Kel, first-order elimination rate constant; Km, concentration required for half of the nonlinear elimination rate (Vmax); k_a_glu, first-order exogenous glucose absorption rate; NE, not estimated; PK/PD, pharmacokinetics/pharmacodynamics; RSE, relative standard error; RVexen, residual variability for exenatide; RVHR, residual variability for HR; RVQT, residual variability for QT; RVGlu, residual variability for glucose; SC50glu/exen, concentration of exenatide required for 50% of the maximum effect; Smaxglu/exen, maximum stimulation of glucose disposition rate by exenatide; Smaxgluisoexen, maximum stimulation of HR production by exenatide; SC50gluisoexen, concentration of exenatide required for 50% of the maximum HR stimulation; V, volume of the central compartment; Vmax, maximum nonlinear elimination rate.

Figure 6. Simulated change in heart rate-corrected QT interval (mQTc) from the premeal time point stratified by treatment (exenatide concentration of 200 pg/mL) and placebo. Figures represent the median individual prediction mQTc following exenatide treatment (triangles) and placebo (circles) following a breakfast meal of 99 g carbohydrates at 6 AM for a subject with a baseline glucose of 92.8 mg/dL, baseline heart rate of 64.1 beats/min, and a baseline QT interval of 393 milliseconds.

a placebo-controlled, 2-arm study, and the baseline-corrected (QTC) was defined as the change from the 6 AM time point (prebreakfast) of the baseline placebo period. The change in the mQTc temporal profile shows a suppression of approximately 10 milliseconds around 2.5 hours after breakfast in the placebo arm and no suppression for the exenatide arm (Figure 6), reflecting the glucose-lowering action of the drug under postprandial conditions. In addition, accounting for glycemic
changes in the QTc interval with the PK/PD model removes any apparent differences in the mQTc between the 2 arms. These simulations illustrate the potential for false-positive signals when confounding factors that can influence the QT interval, such as changes in glucose concentrations under postprandial conditions, are not either experimentally or computationally addressed.

Discussion

There are several nonpharmacological factors that can influence the QT interval that necessitate careful attention to tQT study design and analysis. When one is performing such an analysis of potential drug-induced QT prolongation, it is critical to correct the QT interval for changes in the RR interval. Extensive work has been done to identify the appropriate correction formulas that could be applied. The more commonly used QTc formulas are the Bazett correction formula, the Fridericia correction, and individual correction formulations. Although these standard approaches to normalization or correction remove most confounding variables, temporal elements may continue to complicate analyses of the QT interval, including glucose-insulin dynamics, meal consumption, and diurnal variation. Our previous mathematical model successfully describes the direct and delayed effects of meal consumption and changes in glucose concentrations on the QT interval. In this study we have extended this model to include the PK of exenatide and its effects on glucose and HR. Analysis using the final model shows that drug effects on glucose and HR alone can explain observed changes in the QT interval following exenatide administration, precluding the need to invoke direct drug effects on the QT interval. This modeling approach is particularly important for glucose-lowering agents and for QT study designs that include a meal, both of which may potentially affect the primary assessment period.

In contrast to a formal tQT study with positive control and placebo arms, this study included an intensive PK/PD sampling strategy to assess variables that may confound the QT assessment. The resulting analysis was used to inform the design of a primary tQT study for exenatide. In an effort to avoid the influence of glycemic alterations on the QT interval in the primary tQT study, subjects were given a meal at 6 AM, and QT interval measurements were collected hourly from 9 AM to 3 PM. The primary QT assessment window was defined starting 7 hours postmeal at 1 PM, 2 PM, and 3 PM. In the primary tQT study, suppression of the QT interval in response to the 6 AM meal was still observed at the 9 AM collection point (3 hours postmeal) on all 3 treatment study days. This is consistent with the changes shown in Figure 6, simulations of the impact of meal timing on the suppression of QT shown within this article, and a previous study evaluating the baseline day PD. The authors of the primary QT paper noted that, for the placebo arm, there was a large variation in the change in QTc between early time points in the ECG assessment window, likely due to variables associated with the postprandial response such as insulin and glucose. Furthermore, similar to Figure 6, the variation was less during the exenatide infusion and was attributed to the glucose-lowering effects of exenatide in healthy subjects.

In a traditional QT study in 62 healthy subjects who were given exenatide IR (10 μg twice daily), no clinically significant prolongation of QT relative to placebo was observed. During the ECG assessment phase of that study, subjects fasted overnight for at least 10 hours before each exenatide dose and subsequently received a standardized meal at 4.5 hours postdose. A suppression of QTc was revealed for both the placebo and exenatide treatment arms at 5.5 hours after the meal. The half-life of exenatide is about 2.4 hours, and the plasma drug concentration at the time of the meal (about 4.5 hours postdose) was low and not optimized for glycemic control. Thus, the suppression of the QTc was similar for placebo and exenatide treatment arms. In contrast, the primary tQT study included postprandial exenatide concentrations associated with the IV infusion regimen that were sufficient (eg, 200 pg/mL) to elicit a full glucose-lowering effect, resulting in greater differences between the treatment and baseline period QT measurements.

Within this pilot study, supratherapeutic exenatide concentrations revealed saturable, nonlinear exenatide concentrations that are not associated with typical clinical exposures. Therefore, a nonlinear elimination pathway was added to the previously established linear function describing the elimination of exenatide (Equation 1). Preclinical studies suggest that the nonlinear PK of exenatide might result from target-mediated drug disposition, a case in which binding to the pharmacological target influences the systemic PK. The estimated Km of 453 pg/mL is greater than the maximum plasma concentration (Cmax) associated with the exenatide IR twice-daily formulation as well as the steady-state plasma concentration of 300 pg/mL for the extended-release formulation. The estimated clearance associated with the linear route of elimination is approximately 4.7 L/h. Although greater than what is typically found in subjects with type 2 diabetes, similar clearance values have been reported in healthy volunteers.

For the final model (Figure 2), the effects of exenatide on HR were quantified using an indirect response model. Although an approximate 15-bpm increase in HR was observed, the estimated SC50 for this effect is greater than the mean therapeutic
exenatide concentrations for the weekly formulation and the C_{max} for the IR formulation (584 pg/mL). The model predicts an approximate 9-bpm increase in HR at an exenatide concentration of 208 pg/mL, which is similar to prior observations in healthy subjects. Whereas this effect appears to be consistent in healthy subjects, only a 2- to 4-bpm increase in HR has been observed in patients with type 2 diabetes with long-term exenatide therapy. Furthermore, this increase is found more frequently in patients with low HR at baseline.

The overall model structure is an example of integrating mechanisms of drug action into an underlying dynamical system to effectively deconvolve drug- and system-specific drivers of ultimate physiological responses. This approach is analogous to the PK/PD modeling of compounds acting on induced responses. For example, Lepist and Jusko used 2 linked indirect response models to describe the S-ketoprofen inhibition of carrageenan-induced prostaglandin E_{2} synthesis in several animal species. Modeling the prostaglandin E_{2} response following just S-ketoprofen administration, and failing to jointly consider changes in the underlying system due to carrageenan exposure, could result in model misspecification, parameter identifiability problems, and misinterpretation of drug potency and efficacy. Another example is the PK/toxicodynamic model of the antidotal effects of pralidoxime on paraoxon-induced respiratory toxicity in rats. It is well appreciated that indirect response models are well suited for such systems, and Zhang and D’Argenio have shown how ignoring endogenous feedback control in indirect response models can have a significant impact on the estimation and interpretation of drug potency.

The glucose-lowering effect of exenatide is nearly maximal at the 200 pg/mL target concentration. In addition, an apparent slowing of the glucose absorption rate was observed during the exenatide treatment phase, likely reflecting 1 of the previously identified mechanisms of action of exenatide, namely slowing of gastric emptying. The glucose absorption model was simplified by providing separate k_{a} estimates for each concentration level (day), and further data during the absorption phase of the meal would need to be collected to better quantify the influence of exenatide on gastric emptying. Exenatide suppression of glucose concentrations was defined in the model as a stimulation of the first-order removal of glucose. Supporting mechanisms of action include increased insulin stimulation, suppression of glucagon secretion, and increased satiety. Additional data collected at more time points during the postprandial evaluations and under alternative conditions, including testing in subjects with type 2 diabetes, would be required to more mechanistically quantify the glucose-lowering effects of exenatide.

Conclusions
In summary, the delayed effects of postprandial hyperglycemia on the QT interval need to be considered when designing tQT studies. For therapeutic agents such as exenatide that alter glucose homeostasis, and particularly those that alter postprandial conditions, the QT interval cannot be directly compared to that with placebo without first accounting for confounding factors (eg, glucose and possibly C-peptide concentrations) through PK/PD modeling or by careful consideration of mealtime placement in the study design. Thus, PK/PD models can be critical in the design, analysis, and interpretation of tQT studies, ensuring that the effects observed are directly attributable to the drug and not the result of the intended pharmacological response of the drug under investigation.

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