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ORIGINAL RESEARCH

The Effect of the Once-Daily Human Glucagon-like Peptide 1 Analog Liraglutide on the Pharmacokinetics of Acetaminophen

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ABSTRACT

Introduction: Acetaminophen is a commonly used analgesic and antipyretic drug, and is frequently used to study gastric emptying. Due to its high permeability and high solubility, acetaminophen can be used as a pharmacologic model for medications with similar characteristics. The objective of this study was to assess the effect of liraglutide on the pharmacokinetics (PK) of acetaminophen in patients with type 2 diabetes. ***Methods:*** This was a randomized, placebo-controlled, two-period crossover trial in which subjects with type 2 diabetes received placebo or liraglutide. After steady state PK of liraglutide 1.8 mg/placebo were established, a single dose of acetaminophen 1 g was administered at the time of liraglutide C_{max} (maximum concentration). The PK profile of acetaminophen was assessed at 18 time points during the 8-hour post-dosing period. Placebo and liraglutide were considered equivalent with respect to area under the curve $(AUC)_{0-\infty}$ and AUC_{0-480} min of acetaminophen if the 90% CI for the ratio was fully contained within the limits of 0.80 to 1.25. ***Results:*** All subjects (*n*=18; mean [SD] age 59 [7] years, body mass index [BMI] 29.7 [4.2] kg/m^2, and glycated hemoglobin [HbA_{1c}] 7.8% [0.6%]) completed the study. Equivalence was demonstrated between liraglutide 1.8 mg at steady state and placebo, with respect to acetaminophen $AUC_{0-\infty}$ (estimated ratio 1.04; 90% CI: 0.97, 1.10) and acetaminophen AUC_{0-480} min (estimated ratio 0.95; 90% CI: 0.89, 1.01). During liraglutide, a lower C_{max} was observed (estimated ratio 0.69; 90% CI: 0.56, 0.85) and the median acetaminophen t_{max} occurred 15 minutes later compared with placebo. ***Conclusion:*** The overall exposure of acetaminophen following a 1 g dose was comparable for subjects taking liraglutide or placebo, and the clinical impact of the lower C_{max} and delay in absorption of acetaminophen was considered to be transient and small, and without clinical relevance. No adjustment for acetaminophen is recommended when used concomitantly with liraglutide.

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INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L cells in the lower gut that stimulates endogenous insulin secretion in a physiological and glucose-dependent manner.[1] GLP-1 also decreases blood glucagon levels and slows gastric emptying and motility, while reducing hunger and energy intake.[2-4] In animal models, GLP-1 has been shown to promote beta-cell growth.[5,6] The combination of these mechanisms makes GLP-1 a candidate for the treatment of type 2 diabetes. However, because of the short half-life ($t_{½}$) of endogenous GLP-1,[7,8] a protracted drug substance is required to realize the full therapeutic potential.

Liraglutide is a human GLP-1 analog developed and approved for the treatment of type 2 diabetes. Liraglutide has been developed by combining human GLP-1 with a fatty acid,[9] resulting in a compound with kinetic properties suitable for once-daily injection.[10,11] The mechanism of protraction is mainly down to delayed absorption from the subcutaneous injection site, binding to albumin, and to decreased susceptibility to degradation by dipeptidyl peptidase-4.[12] Liraglutide was shown to provide 24-hour glycemic control and restore beta-cell responsiveness to increasing blood glucose concentrations in patients with type 2 diabetes.[13,14] In addition, longer-term clinical trials have demonstrated that liraglutide treatment is associated with improved glycemic control and body weight reduction.[15-20]

Based on experiments *in vitro*, liraglutide has demonstrated a low potential for pharmacokinetic (PK) drug interactions related to cytochrome P450 and protein binding.[21] However, the slowing of gastric emptying associated with liraglutide could result in modification of the absorption of concomitant, orally administered medications. Acetaminophen is a commonly used analgesic and antipyretic drug, available without prescription. Beyond its clinical use, acetaminophen is often used as a model drug to study gastric emptying.[22] Additionally, it is a drug with high permeability and high solubility, and is characterized as a class I drug according to the Biopharmaceutical Classification System (BCS);[23] therefore, effects on acetaminophen can be used as a pharmacologic model for other medications with similar characteristics.

According to regulatory guidelines for drug-interaction studies,[24,25] it should be tested whether the exposure of the substrate drug (acetaminophen) is changed by the interacting drug (liraglutide). Thus, the evaluation is to be performed during drug-free (or placebo) conditions as well as during the influence of the interacting drug, eg, in a randomized crossover design.

In this study, we set out to test experimentally whether liraglutide at a therapeutic dose level would affect the exposure of acetaminophen in patients with type 2 diabetes.

MATERIALS AND METHODS

Subjects

Adult subjects (aged 18-70 years) with type 2 diabetes, a body mass index (BMI) of 18.5-40.0 kg/m^2, and glycated hemoglobin (HbA_{1c}) of 7.5% to 9.5% (if treated with diet only) or 7.0% to 9.5% (if treated with oral antidiabetic drugs [OADs]) were included

in the study. Subjects were excluded if they had impaired renal or liver function, active cardiovascular disease, hypertension, recurrent severe hyperglycemia, HIV-positive antibody status, active hepatitis B or C, or significant gastrointestinal disease. Any drugs other than nasal sprays, drops used for congestion, or vitamins (excluding mega-dose vitamin therapy, as judged by the investigator) were not allowed within 2 weeks prior to the first dose of study treatment and during the entire trial period. Alcohol or drug abuse within the 12 months prior to the trial and excessive consumption of methylxanthine-containing beverages and foods during the trial were not allowed.

The protocol and informed consent forms were approved by the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Bonn, Germany and by an independent ethics committee, the Ethikkommission der Ärztekammer Nordrhein, Düsseldorf, Germany. The study was performed in accordance with the Declaration of Helsinki. All subjects provided written informed consent prior to trial-related activities.

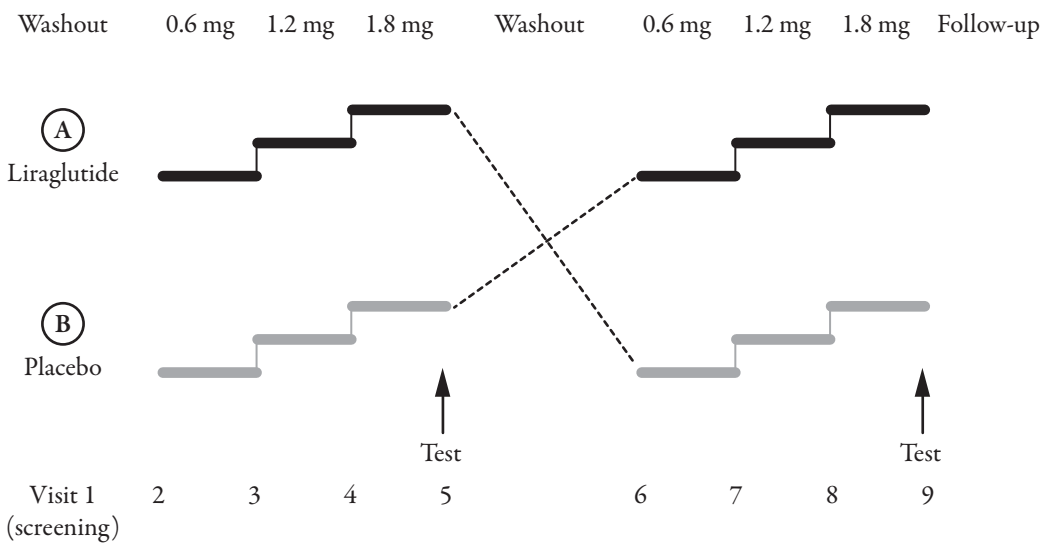
Study Design

This randomized, placebo-controlled, double-blind, two-period crossover trial was conducted at the Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany. The trial compared the effect of liraglutide 1.8 mg versus placebo on PK parameters of acetaminophen.

The once-daily dose of liraglutide (or placebo) was escalated in weekly increments of 0.6 mg until a daily dose of 1.8 mg was reached, with each dose maintained for 1 week (Figure 1). After screening and a washout period of at least 3 weeks for subjects treated with OADs, subjects were randomly assigned to the double-blinded treatment groups A or B (Figure 1).

The investigation for drug–drug interaction (using a single dose of acetaminophen 1 g) was performed the day after the last dose of liraglutide 1.8 mg/placebo, by which time subjects had been treated for a total of 3 weeks, with 1 week at the highest liraglutide (or placebo) dose level, ensuring steady state. After the investigation for drug–drug interaction, a washout period of 3-4 weeks was initiated.

Figure 1. Schematic overview of the trial design.



The subjects then attended the clinic again for initiation of the new 3-week treatment period with placebo or liraglutide. At the end of the second 3-week treatment period, the investigation for drug–drug interaction was repeated. Subjects attended the clinic for all visits related to dose initiation, dose escalation, or investigation for drug–drug interaction. From 48 hours prior to and during the investigation for drug–drug interaction, the subjects were asked to abstain from strenuous exercise, alcohol, and beverages and food containing methylxanthine (such as coffee or tea).

Trial Products

Liraglutide and placebo were administered subcutaneously in the abdomen once daily in the evening using a prefilled pen device (3 mL FlexPen®, Novo Nordisk A/S, Copenhagen, Denmark).

For the investigation of drug–drug interaction, acetaminophen 1 g (two Benuron® 500 mg tablets, Novartis, Basel, Switzerland) was used.

Test Day and Sample Collection

The drug–drug interaction investigations with acetaminophen were performed at the end of each 3-week treatment period. The last liraglutide dose was to be given at 11:00 PM the evening before the investigation for drug–drug interaction. Blood samples for liraglutide bioanalysis were taken at 6, 8, 10, and 12 hours post dose in order to assess the adherence to liraglutide treatment.

In the morning, 8 hours after the liraglutide dose (around time to peak concentration [t_{max}] for liraglutide[10]), acetaminophen 1 g was ingested with 100 mL of water. Blood sampling to measure plasma acetaminophen was performed immediately prior to the acetaminophen dose (time: 0 minutes) and frequently during the 8-hour post-dosing period (time: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 90, 120, 180, 240, 360, and 480 minutes post dose). The subjects were served a standard lunch 5 hours post dose.

Study Endpoints

The primary study endpoint for plasma acetaminophen PK included area under the curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$). As $AUC_{0-\infty}$ could not be calculated for all profiles, it was decided to categorize AUC from time 0 to 480 minutes ($AUC_{0-480\ min}$) as a co-primary endpoint prior to unblinding the data, as this would allow inclusion of data from all subjects. Other PK endpoints for plasma acetaminophen included C_{max} , t_{max}, and apparent $t_{½}$.

The concentration of acetaminophen in plasma was determined by AAIPharma Deutschland GmbH & Co KG (Neu-Ulm, Germany; now Nuvisan Pharma Services). Acetaminophen and internal standards (1000 ng/mL acetaminophen-D4, TRC Canada, North York, Ontario, Canada) were separated from serum by a liquid/liquid extraction, and were analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS). Chromatography was carried out on a Phenomenex (Macclesfield, UK) Synergi Polar RP, 200×2.0 mm, 4 µm column and the column effluent was monitored by multiple-reaction monitoring using a PE Biosystems (now Applied Biosystems, Foster City, CA, USA) SCIEX API 3000 mass spectrometer. The overall precision (expressed as coefficient of variation, CV) and accuracy (expressed as bias) of quality controls and standards was better or equal to 8.7% for all concentrations. The quantification was performed against a calibration range, which is linear from 250 ng/mL (lower limit of quantification [LOQ]) to 20,000 ng/mL (upper LOQ).

The concentration of total liraglutide in plasma was analyzed by Capio Diagnostik A/S (now Unilabs, Geneva, Switzerland), using a validated specific enzyme-linked immunosorbent assay (ELISA) developed at Novo Nordisk and described by Agersø et al.[10] The method had a lower LOQ of 18 pmol/L, a detection limit of 3 pmol/L, and an upper LOQ of 4440 pmol/L.

Safety assessments

Safety was assessed by adverse events, hypoglycemic episodes, physical examination, vital signs, electrocardiogram (ECG) and laboratory parameters (hematology, biochemistry, and urinalysis).

Statistical Analysis

The minimum number of subjects to complete the trial was 16 in order to have a power of 0.9 in the investigation for drug–drug interaction (equivalence test of $AUC_{0-\infty}$). This calculation was based on the assumption of an intrasubject standard deviation of log ($AUC_{0-\infty}$) of acetaminophen of 0.18.

PK parameters ($AUC_{0-480\ min}$, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$) were derived from the plasma acetaminophen concentration data for each individual using noncompartment methods. AUCs were calculated by the linear trapezoidal method. $AUC_{0-\infty}$ was derived as $AUC_{0-t}+AUC_{t-\infty}$, where $AUC_{t-\infty}$ was approximated by the area from time (t) to infinity under an exponential curve.

Before unblinding the data, eight acetaminophen profiles were excluded from the estimation of $AUC_{0-\infty}$ as these had a prolonged elimination phase. For four of these profiles the terminal elimination rate constant (λ_z) was not calculated, as only one time point after t_{max} was observed. For the remaining four profiles $\lambda_z$was calculated, but not applied for calculation of AUC as the predicted area provided more than 20% of the total AUC. However, in parallel, it was decided to categorize AUC from $AUC_{0-480\ min}$ as a co-primary endpoint prior to unblinding the data as this would allow inclusion of data from all subjects. The eight profiles were all from subjects treated with liraglutide 1.8 mg. Thus, the number of profiles used for calculation of $AUC_{0-\infty}$ and the secondary endpoint, $t_{½}$, was less than 18 for liraglutide (n=10 for $AUC_{0-\infty}$; n=14 for $t_{½}$). The parameters $AUC_{0-480\ min}$, t_{max} and maximum drug concentration (C_{max}) were estimated from all profiles.

The exposure of acetaminophen after administration of either liraglutide or placebo was considered equivalent if the 90% CIs for the $AUC_{0-\infty}$ and $AUC_{0-480\ min}$ ratios were fully contained in the interval from 0.8 to 1.25. Analysis of variance (ANOVA) based on the logarithmic transformed values was applied for comparisons between treatments. The model included fixed effects of treatment (liraglutide/placebo) and period (first/second) and a random effect of subject.

The λ_z was estimated by log linear regression on the terminal log linear part of the concentration–time curve, and was used to calculate $t_{½}$. Statistical analysis of the additional PK endpoints C_{max} and $t_{½}$ were performed using ANOVA.

The analysis of t_{max} was performed by use of a nonparametric method. The difference between treatments and the 90% CI was estimated using the Hodges-Lehmann estimator.

Sensitivity analyses of AUC and $t_{½}$ were performed in order to evaluate the potential impact of not having estimated $t_{½}$ for four profiles and AUC for eight profiles. Missing values of $t_{½}$ were imputed by estimates of $t_{½}$ based on only two observations, namely t_{max} and the succeeding value. These estimates were considered to provide conservative estimates

of $t_{½}$, as they were calculated based on a period closer to t_{max} than the remaining profiles, and therefore more affected by ongoing absorption. Based on these imputed values of $t_{½}$, conservative estimates of AUC were calculated, and all values of AUC were included in the analysis.

RESULTS

Subject Demographics

A total of 18 subjects with type 2 diabetes (14 males and four females) were included in and completed the study. All subjects were Caucasian. The subjects had the following baseline characteristics (mean±SD); age 59±7 years (range 48-70 years), body weight 91.0±15.9 kg (range 67.2-125.7 kg), height 1.75±0.07 m (range 1.64-1.86 m), BMI 29.7±4.2 kg/m² (range 23.5-37.5 kg/m²), and HbA_{1c} 7.8%±0.6% (range 7.0% to 9.0%). One subject demonstrated measurable concentrations of liraglutide in plasma during treatment with placebo and the acetaminophen profile for this subject was excluded from the analysis.

Pharmacokinetics

Figure 2 shows the mean plasma acetaminophen concentration–time curves during liraglutide 1.8 mg and placebo. The results of the primary PK analyses demonstrated that the acetaminophen $AUC_{0-\infty}$ and $AUC_{0-480\ min}$ at liraglutide steady state were equivalent between subjects treated with liraglutide 1.8 mg and subjects treated with placebo, as both 90% CIs were fully contained within the interval from 0.8 to 1.25 (Table 1).

The results of the additional PK analyses demonstrated that the administration of liraglutide resulted in a decreased C_{max} of acetaminophen (31%) and a slightly delayed tmax of acetaminophen (median difference of 15 minutes) when compared with placebo (Table 1). The apparent $t_{½}$ was longer with liraglutide than with placebo.

The sensitivity analysis where missing values of $t_{½}$ were imputed with conservative estimates, and where no values of $AUC_{0-\infty}$ were omitted, confirmed the results regarding $AUC_{0-\infty}$ and $t_{½}$. The estimated ratio for $AUC_{0-\infty}$ was

Figure 2. Mean plasma concentrations of acetaminophen following a single dose of acetaminophen 1 g with once-daily liraglutide 1.8 mg or placebo in subjects with type 2 diabetes (n=18 for liraglutide; n=17 for placebo).

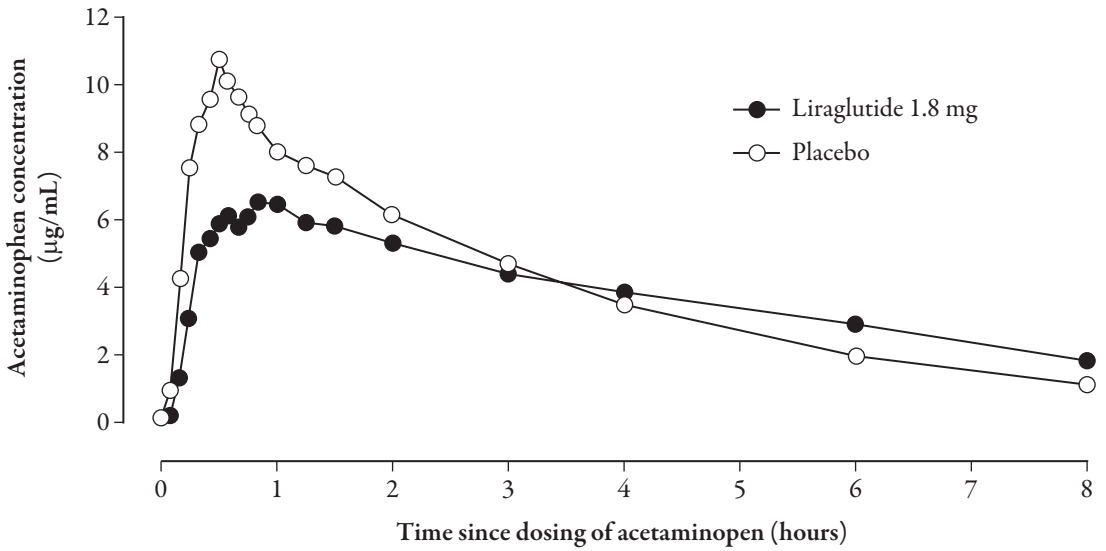


Table 1. Pharmacokinetic (PK) parameters of acetaminophen following a single dose of acetaminophen 1 g with liraglutide 1.8 mg or placebo injections in subjects with type 2 diabetes.

PK parameter	Liraglutide 1.8 mg (*n*=18), mean±SD	Placebo (*n*=17), mean±SD	Estimated ratio (90% CI)*
$AUC_{0-\infty}$, µg/min/mL	2020±315†	2243±659	1.04 (0.97, 1.10)
$AUC_{0-480\ min}$, µg/min/mL	1869±452	1989±525	0.95 (0.89, 1.01)
C_{max}, µg/mL	9.54±4.68	12.86±5.93	0.69 (0.56, 0.85)
t_{max}, min‡	48	30	15 (0.0, 92.5)
$t_{½}$, min	180±77§	144±25	1.23 (1.10, 1.38)

AUC=area under the curve; SD=standard deviation.
*The PK parameters after administration of either liraglutide or placebo were considered equivalent if the 90% CI was fully contained in the interval from 0.8 to 1.25.
†Calculation of $AUC_{0-\infty}$ with liraglutide was based on *n*=10.
‡Median values and difference for t_{max} between treatments are shown. The 90% CI was estimated using the Hodges-Lehmann estimator.
§Calculation of $t_{½}$ with liraglutide was based on *n*=14.

1.12 (1.04-1.20) and the estimated ratio for $t_{½}$ was 1.31 (1.15-1.48).

Safety

Liraglutide was well tolerated. There were no withdrawals because of adverse events, and no hypoglycemic episodes or serious adverse events reported during the trial period. A total of 18 adverse events were reported by nine subjects, and the same number of adverse events emerged during liraglutide (nine adverse events in seven subjects) and placebo treatments (nine adverse events in five subjects). The majority of events were mild, and the most frequent adverse events were headache, gastrointestinal disorders, and infections. There were no changes reported in physical examinations, vital signs or ECGs, and no trends for changes in any of the laboratory parameters were identified.

DISCUSSION

Acetaminophen 1 g is a commonly administered dose that can be expected to produce adequate plasma drug levels to assess any potential interaction. The maximum concentration of acetaminophen is reached in 30-60 minutes. The terminal elimination $t_{½}$ of acetaminophen is approximately 2 hours.

In the present study, administration of liraglutide did not alter the overall exposure of acetaminophen. However, liraglutide caused a minor decrease in and delay of the peak concentration, which is in agreement with the well known slowing effect of GLP-1 on gastric emptying.[3,4] This study was designed to investigate the effect of the administration of liraglutide on the highest approved dose level (1.8 mg) versus placebo on the PK properties of orally administered acetaminophen. Thus, the effect shown in this study is not expected to be exceeded during clinical use.

Using acetaminophen to investigate drug–drug interactions and gastric emptying is a well established approach.[22,26,27] Furthermore, acetaminophen is a commonly used analgesic and antipyretic drug, available over the counter. A crossover design was chosen to reduce interindividual patient variability and patient numbers. The trial design adhered to the guidelines for drug interaction studies.[24,25]

The 1.8-mg dose of liraglutide has been approved for the treatment of type 2 diabetes and was used as the highest dose in the phase 3 trials with liraglutide, where it was found to be both efficacious and safe.[15-19] Dose escalation of liraglutide has been shown to mitigate gastrointestinal side effects,[28] and, in accordance with approved clinical use, the dose-escalation schedule of 1 week per dose level was used for liraglutide. Steady state for liraglutide is reached after 3 days of treatment with liraglutide.[29] Administering liraglutide to steady state at the highest dose level in this study increased the possibility for detecting a potential interaction with acetaminophen.

Administration of acetaminophen around the time of C_{max} at steady state for liraglutide 1.8 mg resembles the time at which the highest concentrations of liraglutide would appear. During these conditions, equivalence with regard to the overall exposure of acetaminophen, presented as $AUC_{0-\infty}$ and $AUC_{0-480\ min}$ was shown for both treatments. However, the statistical analysis demonstrated that C_{max} of acetaminophen was 31% lower after liraglutide treatment compared with placebo and the t_{max} for acetaminophen was estimated to occur 15 minutes later during treatment with liraglutide compared with placebo. These results were also reflected in a longer apparent $t_{½}$ for subjects treated with liraglutide and compared with placebo. Limitations of the study relate to $t_{½}$, which could not be calculated for several of the profiles following administration with liraglutide, which may bias the evaluation of this parameter (based on a lower number of subjects) towards a shorter $t_{½}$ and, therefore, potentially also bias the evaluation of $AUC_{0-\infty}$ downwards. A sensitivity analysis where missing values of $t_{½}$ were imputed with conservative estimates, and where no values of AUC were omitted, resulted in a slightly larger ratio in $t_{½}$ between liraglutide and placebo and, in agreement with this, a slightly larger ratio in AUC. The sensitivity analysis, however, confirmed the equivalence in AUC between liraglutide and placebo.

The reduced C_{max} and delayed t_{max} of the orally administered acetaminophen suggest a delayed rate of initial absorption, which would be associated with an early slowdown in gastric emptying during a standardized meal test. However, in the present study, the overall AUC was not changed by liraglutide and the effects on acetaminophen kinetics were, as expected, based on the well known effects of native GLP-1[30-32] and other findings with liraglutide.[30]

In the trial presented in this paper, the effect of liraglutide on acetaminophen concentration during a standard meal was also evaluated using the same study set up and patients.[30] At steady state for liraglutide 1.8 mg, similar effects on acetaminophen concentrations after oral intake were observed when taken with a meal, as shown by a 6% reduction of $AUC_{0-300\ min}$, a 23% reduction of C_{max}, and a 20-minute delay of t_{max} compared with placebo.[33] Thus, the effect of liraglutide on acetaminophen concentration after oral intake is similar with and without food intake.

These results are consistent with results of liraglutide use with other orally administered drugs. When given concomitantly with steady state liraglutide 1.8 mg, the exposure of drugs from BCS class II-IV were found to be equivalent (atorvastatin and griseofulvin) or with a minor decrease (lisinopril and digoxin) to placebo treatment.[34] Furthermore, a 27% to 38% lower Cmax and a delay of 1-2 hours was observed for atorvastatin, lisinopril, and digoxin, and a higher C_{max} and unchanged t_{max} were observed for griseofulvin. However, none of the effects was considered clinically significant.[21,33]

In a study comparing acetaminophen PK during exenatide (10 µg) and placebo injections given with different time intervals

relative to acetaminophen dosing, it was found that with exenatide injections, mean plasma acetaminophen exposure ($AUC_{0\text{-}12\ h}$) values were reduced by 11% to 24% compared with placebo.[26] Maximum plasma acetaminophen concentration was similar to placebo conditions if the administration of acetaminophen occurred before the exenatide injection, but reduced by 37% to 56% if acetaminophen was given at the same time or up to 4 hours after the injection of exenatide. This is at best similar to the effect of liraglutide 1.8 mg and somewhat more pronounced when the acetaminophen was administered 1-4 hours after the exenatide injection.

In the exenatide study, acetaminophen tmax (average) was delayed by 150% to 700% (or 0.9-4.2 hours) if acetaminophen was administered at the same time or up to 4 hours after exenatide dosing.[26] This corresponds to a similar or larger delay than the present study, in which liraglutide t_{max} (median) occurred 15 minutes later compared with placebo. These results confirm the delaying effect of gastric emptying with GLP-1 receptor agonists. The conclusion from the study with exenatide was that the overall acetaminophen exposure was not affected in a clinically meaningful way. The effects on acetaminophen exposure, C_{max} and tmax observed with liraglutide 1.8 mg, are on par with or less than with exenatide and therefore the results of the current study would also suggest that the pharmacokinetics of acetaminophen are not affected in a clinically relevant manner during liraglutide treatment.

In another study, the effect after 2 weeks of treatment with exenatide (1 week on 5 µg and 1 week on 10 µg, twice daily) or sitagliptin (100 mg once daily) on acetaminophen concentrations after oral intake during a standardized meal test was investigated.[35] For the standardized meal test, exenatide was dosed 15 minutes before and sitagliptin was dosed 30 minutes before meal and acetaminophen intake. The results confirmed a suppression of $AUC_{0\text{-}240\ min}$ (acetaminophen) to 56% on average of exenatide compared with sitagliptin, which did not alter the acetaminophen concentrations compared with pre-dose assessments, demonstrating the ability of GLP-1 receptor agonists to slow gastric emptying.[35]

Liraglutide was well tolerated in this study, as demonstrated by no withdrawals from treatment and no safety concerns raised. No hypoglycemic events were reported, which is in line with the glucose-dependent insulinotropic effect of liraglutide. Therefore, from these data it can be concluded that the adverse-event profile of liraglutide was comparable to placebo.[36]

The exposure of acetaminophen following a 1-g dose was comparable for subjects taking liraglutide or placebo, and the clinical impact of the lower C_{max} and delay in absorption of acetaminophen was considered to be transient and small, and without clinical relevance. Therefore, no dose adjustment for acetaminophen is recommended when used concomitantly with liraglutide.

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the work as a whole. Clinical trial registration number: EudraCT 2006-000561-10.

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