The Lidose Hard Capsule Formulation of Fenofibrate is Suprabioavailable Compared to the Nanoparticle Tablet Formulation Under High-fat Fed Conditions

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ABSTRACT – Purpose: The therapeutic equivalence of multiple registered fenofibrate formulations, several of which are suprabioavailable and therefore marketed at lower dosage strengths than their reference products, is based on the results of bioequivalence studies. Most of these formulations show a higher bioavailability when taken with a high-fat meal. The relative bioavailability of two of these formulations, the 200 mg Lidose hard capsules and the 145 mg nanoparticle tablets, was assessed when taken with a high-fat meal. **Methods:** In this single dose, 2-way, randomized, crossover study, 24 healthy subjects received a 200 mg fenofibrate Lidose hard capsule (Test) and a 145 mg nanoparticle tablet (Reference) under high-fat fed conditions. Plasma concentrations of fenofibric acid were measured up to 72 hours by using a validated LC-MS/MS method. **Results:** The geometric mean ratios (Test/Reference) and the 90% confidence intervals for AUC_{0-t} and C_{max} were 1.37 (131.58 – 142.88) and 1.38 (124.60 – 152.93), respectively. The median (range) T_{max} values of fenofibric acid were 4.5 h (3.0 – 8.0 h) and 3.25 h (1.0 – 6.5 h) after administration of the Lidose hard capsule and the nanoparticle tablet, respectively. **Conclusion:** Under high-fat fed conditions the extent of fenofibrate absorption was 37% higher for the 200 mg Lidose hard capsule compared to the 145 mg nanoparticle tablet, which is exactly as expected based on a mg-to-mg weight basis. The results of the present study underline the importance of assessing bioequivalence of fenofibrate formulations under identical fed conditions, and preferentially after a high-fat meal as this condition represents the worst-case scenario. Furthermore, the results of this study demonstrate that the 145 mg nanoparticle tablet is not bioequivalent to the 200 mg Lidose hard capsule when administered under high-fat meal conditions.

INTRODUCTION

Fenofibrate is indicated for use in the treatment of primary hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia in adults who have not responded to non-pharmacological measures. Its lipid-modifying effects are mediated by activation of peroxisome proliferator-activated receptor-α (1,2). The European Commission (European Referral) also endorsed in 2010 an additional indication for fenofibrate, i.e. mixed hyperlipedemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL- cholesterol are not adequately controlled. Fenofibrate was the only fibrate to receive this indication based on the results of the ACCORD-LIPID study (3). Fenofibrate is the isopropyl ester of fenofibric acid (4). It is a prodrug which, following oral administration, is rapidly hydrolyzed by esterases to its active metabolite, fenofibric acid. Unmetabolized fenofibrate has been reported to be undetectable in plasma samples following oral administration (5).

Fenofibrate has been marketed since 1975 (6,7). It is a substance with poor water solubility and the original formulation was a 100 mg tablet to be taken as 3 tablets at the same time, because fenofibrate had a poor oral bioavailability. It was also recommended to be taken with food to increase the extent of absorption (7). A 200 mg capsule formulation of micronized fenofibrate was subsequently developed as well as a 160 mg micronized fenofibrate microcoated tablet.

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By using smaller fenofibrate particle sizes these newer formulations showed improved bioavailability (suprabioavailability) and were registered at lower dose strengths compared to the initial formulations (7). SMB-Galephar (Brussels, Belgium) developed a 200 mg hard capsule formulation with a semi-solid content (Lidose, patent EP 0801562B1) into which fenofibrate is homogeneously dispersed within a lipid excipient mixture (7). This product was considered to be bioequivalent to the 200 mg micronized fenofibrate reference product on the basis of a crossover relative bioavailability study (8). A major drawback of all these fenofibrate formulations is that adequate oral absorption requires their administration with a *high-fat meal* (9-11). More recently, a new nanoparticle tablet formulation of fenofibrate has become available in 48 mg and 145 mg dose strengths (12,13). Unlike previous fenofibrate formulations, the oral bioavailability of this nanoparticle formulation was apparently not affected by food and, consequently, it has been recommended that this nanoparticle formulation can be administered without regard to food intake (12,13).

Differences in bioavailability of the various fenofibrate formulations mean that they are not equivalent on a milligram-to-milligram basis. Consequently, marketed oral fenofibrate formulations may not only differ substantially in available dose strengths, but also in the requirement to be taken with a meal (9). The present bioequivalence study was undertaken to investigate the bioavailability of a 145 mg fenofibrate nanoparticle tablet relative to the 200 mg fenofibrate Lidose hard capsule when administered to healthy volunteers under high-fat conditions.

METHODS

Subjects and study protocol

The study protocol was approved by the Ethics Committee of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania. The study was performed in accordance with the version of the Helsinki Declaration in force at the time of the study and Good Clinical Practice Guidelines. The clinical part of the study was conducted by S.C. Kynetyx HT S.R.L., Cluj-Napoca, Romania. Twenty-four healthy non-smoking subjects (12 males and 12 females) between the age of 18 and 36 years (24.7 ± 4.7 years, mean ± SD), having a body mass index between 18.8 and 27 kg/m^2 (22.3 ± 2.6 kg/m^2) were included after having undergone a complete medical examination (clinical observation, ECG, haematological, biochemical, and serological screening). Written informed consent was obtained for every subject prior to enrolment.

Study design

The study was designed as a single dose, open label, two-period, two-treatment, two-sequence, crossover study to compare the bioavailability of two oral fenofibrate formulations: Fenogal Lidose hard gelatin capsules containing 200 mg fenofibrate (Laboratoires SMB, Brussels, Belgium) versus LipanthylNano film-coated tablets containing 145 mg fenofibrate as nanoparticles (Abbott Products, Belgium). The two study periods were separated by a washout of minimum 8 days. An equal number of subjects was randomly assigned to each of the two possible administration sequences. During each study period, subjects were admitted to the clinical facility in the evening prior to the administration. One 200 mg fenofibrate Lidose hard gelatin capsule (Test) or one 145 mg fenofibrate nanoparticle tablet (Reference) was administered with 240 ml of water 30 minutes after the start of a high fat, high calorie breakfast. Water was allowed ad libitum except for one hour before and one hour after drug administration. Standard meals were given at 4 h (lunch), 8 h (snack) and 13 h (dinner) following dosing. Study subjects were confined to the clinical center from the evening before until 24 hours after dosing. A total of twenty-two 6-ml blood samples were collected per period: pre-dose (-0.35 h), and 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.25, 4.5, 4.75, 5.0, 5.25, 5.5, 5.75, 6.0, 6.5, 7.0, 8.0, 12, 24, 48 and 72 hours following administration. Subjects were monitored for adverse events throughout the course of the study until 30 days

Drug Analysis

Fenofibric acid plasma concentrations were determined by liquid chromatography coupled to a tandem mass spectrometry detection system (LC-MS/MS, API 3000, AB Sciex, Toronto, Canada). In short, to 40 µl of plasma were added 460 µl of methanol, containing deuterated fenofibric acid (d6-fenofibric acid) as internal standard. An aliquot of the supernatant was injected onto an end-capped dodecylsilica column (Synergi Max-RP, 80 Å pore size, 4 µm particle size, 150 mm x 2 mm internal diameter, Phenomenex). The mobile phase, consisting of a mixture of acetonitrile, methanol and an aqueous

solution of 5 mM ammonium acetate adjusted to pH of 4.5 with acetic acid (37.5:37.5:25, v/v/v), was delivered to the column at a flow rate of 0.2 ml/min. Mass spectrometric detection was carried out using an Applied Biosystems API 4000 Triple Quadrupole instrument (Thornhille, Toronto, Canada) equipped with a TurbulinSpray interface. The MS/MS ion transitions monitored were m/z 317.1 → 230.8, and 323.1 → 230.7 for fenofibric acid and d6-fenofibric acid, respectively. The lower limit of quantification of fenofibric acid in plasma was 0.2502 µg/ml. Details of the analytical method are described elsewhere (12). The bioanalytical method was validated regarding selectivity, accuracy, precision, stability, back-conversion and matrix effect to comply with the EMA guidelines (11). Incurred sample reanalysis showed that 97.9% of the reanalysed samples were within 20% of the mean.

Pharmacokinetic analysis

Pharmacokinetic parameters of fenofibric acid were obtained by non-compartmental analysis. C_{max}, the maximum plasma concentration, and T_{max}, the time to reach C_{max}, were obtained directly from the observed fenofibric acid plasma concentration-time data. AUC_{0-t} (area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration) was calculated by using the mixed linear-log trapezoidal method (Kinetica®, version 5.0, Thermo Fisher Scientific). Total area under the curve ($AUC_{0-\infty}$) was obtained as the sum of AUC_{0-t} and the extrapolated area under the curve ($AUC_{t-\infty}$), which was calculated by dividing the fitted last quantifiable plasma concentration by $0.693/t½$, and t½ (the terminal plasma half-life of fenofibric acid) was estimated from the slope of the terminal phase of the semi-logarithmic plasma concentration versus time curve.

STATISTICAL ANALYSIS

Statistical evaluations of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were performed after ln-transformation using ANOVA for a two-way crossover design. After the 4 dropouts the sequence for the remaining 20 subjects was still balanced (21). The general linear model (GLM) procedure was used to assess the effect of sequence, subject nested within sequence, period and formulation on these BE metrics (Kinetica®, version 5.0, Thermo Fisher Scientific and EquivTest/PK®, Statistical Solutions, 2006, gave the same results). For the assessment of bioequivalence, the 90% confidence intervals were calculated around the geometric mean ratio Test/Reference according to the two one-sided tests procedure of Schuirmann (14). Bioequivalence was concluded when the 90% confidence interval for the primary bioequivalence metrics AUC_{0-t} and C_{max} fell within the 80-125% acceptance limits (15). T_{max} is not considered a primary metric for bioequivalence assessment, but it was nevertheless analysed by the non-parametric Friedman test. Descriptive results are expressed as mean ± standard deviation for continuous variables (e.g. C_{max}, AUC) and median (range) for the discrete variable T_{max}.

Safety assessment

Vital signs (blood pressure, heart rate) were recorded for each subject at screening, throughout the confinement periods and at the end of the study. Laboratory safety parameters (urinalysis, hematology, clinical chemistry) were measured at screening and at the end of the study. All study subjects were monitored for adverse events throughout the entire confinement periods and until 30 days after the administration of the last dose.

RESULTS

After screening, 24 subjects were randomised to receive a single dose of the test and reference fenofibrate formulations. One subject withdrew before the start of the study, another subject dropped out during period I, and 2 subjects withdrew from the study during period II. As a result, the pharmacokinetic and statistical analyses are based on the results of the 20 study subjects who completed both phases of the study. The mean fenofibric acid plasma concentration-time profiles following administration of a single dose of the test (T) and reference (R) prepration are shown in figure 1. Pharmacokinetic parameter estimates of fenofibric acid are summarized in Table 1. Peak plasma concentrations of fenofibric acid were reached at 4.5 h (3.0 h – 8.0 h) [median (range)] following administration of test formulation, and at 3.25 h (1.0 h – 6.5 h) following administration of reference formulation. The difference in T_{max} between Test and Reference formulation was not statistically significant (Friedman test). The plasma half-life of fenofibric acid was 18.6 h (range: 7.3 – 28.6 h) and 18.7 h (range: 6.4 – 28.4 h) for Test and Reference formulation, respectively. On average

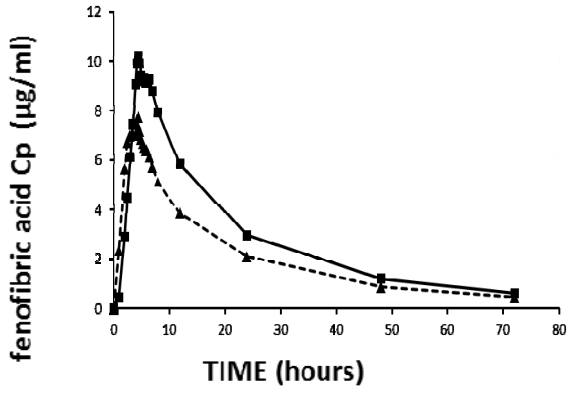

Figure 1. Mean fenofibric acid plasma concentration-time profiles in 20 healthy subjects after single dose administration of a 200 mg fenofibrate Lidose hard capsule (■——■; Test preparation) and a 145 mg fenofibrate nanoparticle tablet (▲- - - - - - - -▲; Reference formulation).

8.0 ± 3.5% (Test formulation) and 8.6 ± 3.4% (Reference formulation) of the total area under the curve ($AUC_{0-\infty}$) was located in the extrapolated part (i.e. $AUC_{t-\infty}$). The geometric mean ratios (T/R) and 90% confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are summarized in Table 2. The intra-individual variability (CV_{anova}) of C_{max} was 18.9%, and was smaller for AUC_{0-t} (7.5%) and $AUC_{0-\infty}$ (7.9%) (Table 2).

A total of 8 treatment emergent adverse events were reported by 7 subjects in the study. Six of them were reported with the 145 mg nanoparticle tablets, and 2 were reported with the 200 mg Lidose hard capsules. Five adverse events were of mild intensity and 3 were of moderate intensity. Four adverse events (all reported with the 145 mg nanoparticle tablets) were considered related with the study drug. The most common treatment-related adverse event was headache. No serious adverse events occurred during the study.

DISCUSSION

Fenofibrate was first introduced in 1975 but the oral bioavailability of this standard formulation was very low especially when taken without a high-fat meal (6,9). Micronized fenofibrate formulations were subsequently developed to increase the water solubility and hence the oral bioavailability of fenofibrate (2). A micronized fenofibrate capsule formulation was introduced in Europe in 1992, but was later replaced by a micronized microcoated tablet with a 25% increase in bioavailability compared to the micronized capsule formulation. The Lidose drug delivery technology, i.e. a hard capsule with a semi-solid content into which fenofibrate is homogeneously dispersed within a lipid excipient mixture, was also used in an attempt to improve the oral fenofibrate bioavailability (9). Despite improvement in oral bioavailability of the micronized fenofibrate tablets and Lidose fenofibrate hard capsules, these formulations still require the presence of food, particularly a high-fat meal, to maximize the extent of fenofibrate absorption (2,9). More recently, fenofibrate formulations based on nanoparticle technology were developed in an attempt to reduce or completely eliminate the food effect (1,9). Ling et al. has published a detailed description of the currently available fenofibrate and fenofibric acid formulations and the effect of food on their oral bioavailability (9).

Table 1. Mean ± SD (median and range for T_{max}) values for the relevant pharmacokinetic parameters of fenofibric acid following single dose administration of Test (200 mg Lidose hard capsules) and Reference formulation (145 mg nanoparticle tablets) to 20 healthy subjects.

Parameter	***TEST*** ***200 mg Lidose capsules***	***REFERENCE*** ***145 mg nanoparticle tablets***
T_{max} , h	4.5 (3.0–8.0)	3.25 (1.0–6.5)
C_{max} , µg/ml	12.6±2.9	9.2±2.3
AUC_{0-t} , µg.h/ml	193.3± 84.9	138.8±51.3
$AUC_{0-\infty}$, µg.h/ml	211.9±101.0	153.2±63.4
t½ , h	18.8±5.8	18.8±5.6

Table 2: Geometric mean ratios (GMR) T/R, 90% confidence intervals (90% CI) and intrasubject variabilities (CV_{anova}) for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ following single dose administration of Test (200 mg Lidose hard capsules) and Reference formulation (145 mg nanoparticle tablets) to 20 healthy subjects.

BE parameter	***GMR***	***90% CI***	***CV_{anova} (%)***
C_{max} , µg/ml	1.38	124.60–152.93	18.9
AUC_{0-t}, g.h/ml	1.37	131.58–142.88	7.5
$AUC_{0-\infty}$, µg.h/ml	1.36	130.38–142.08	7.9

During the development of these different formulations to optimize the extent of fenofibrate absorption and to suppress the food effect, bioequivalence studies were carried out to show therapeutic equivalence between the marketed reference formulation and the newly developed, often suprabioavailable, formulations. Unfortunately, these bioequivalence studies were not always carried out under the same fed condition. For example, the 48 mg and 145 mg fenofibrate nanoparticle tablets were shown to be bioequivalent to the 200 mg micronised fenofibrate capsule under low-fat conditions (18). However, for both the 48 mg and 145 mg nanoparticle tablets, the AUC_{0-t} of fenofibric acid was on average 13% lower compared to the 200 micronized capsule formulation. Bioequivalence could still be demonstrated because the intra-individual variability of the AUC for fenofibric acid was low and a large number of subjects was used (72 subjects were enrolled and 68 completed the study) (18). Since the extent of the food effect may be affected by the fat content of the meal, the unanswered question is whether under high-fat fed conditions the 145 mg nanoparticle tablet would still have been bioequivalent to the 200 mg micronized capsule. On the other hand, in a randomized, 3-way, food-effect study on the 145 mg nanoparticle tablet, it was shown that the relative bioavailability following administration with a low-fat and a high-fat meal was very similar to that after administration of the nanoparticle formulation on an empty stomach (12,18).

When the bioavailability of a 67 mg and 200 mg Lidose hard capsules was compared to that of the 67 mg and 200 mg micronized fenofibrate capsules, the Lidose 67 mg and 200 mg formulations were shown to be bioequivalent to the 67 mg and 200 mg micronized fenofibrate capsules, respectively, under *high-fat fed* conditions (8). In the bioequivalence study described in this publication, the bioavailability of a 145 mg fenofibrate nanoparticle tablet was compared to that of a 200 mg fenofibrate Lidose hard capsule under *high-fat fed conditions*. Based on the results of the above described bioequivalence studies (8,18) in which both the 145 mg nanoparticle tablets and the 200 mg Lidose formulations were demonstrated to be bioequivalent to the same reference i.e. a 200 mg fenofibrate micronized capsule, but in different studies, one would expect the 200 mg Lidose capsules to be bioequivalent to the 145 mg nanoparticle Lipanthyl® tablets. However, the results of the present study showed a 37% higher extent of fenofibrate absorption for the 200 mg Lidose capsules compared to the 145 mg nanoparticle tablets. In fact the 200 mg Lidose formulation showed an equivalent AUC on a weight-to-weight basis compared to the 145 mg nanoparticle formulation.

During the last 20 years several reformulations of the marketed branded fenofibrate preparations have been developed as well as generics of out of patent fenofibrate preparations. Registration of these reformulated and generic fenofibrate preparations was based mainly on bioequivalence studies to show therapeutic equivalence between the reformulated or generic preparation and a marketed reference formulation. In a recent paper by Downing et al., the authors show how Abbott Laboratories, the maker of branded fenofibrate, has produced several suprabioavailable reformulations in a successful attempt to maintain a dominant market share by preventing generic competition (19). This has resulted in a situation where many different fenofibrate formulations are on the market, not necessarily possessing the same dose strengths because some are suprabioavailable compared to others (9,19). In addition, for some of these fenofibrate formulations it is claimed that there is no food effect, although the various bioequivalence studies have certainly not been carried out under the same fed conditions. The EMA and the FDA recommend to use a high-calorie, high-fat meal during food effect bioavailability and bioequivalence studies because such meal is expected to provide the greatest effects on gastrointestinal physiology and hence on the bioavailability characteristics of the test formulation (15,20). In addition, for fenofibrate administration the situation is

complicated by the fact that the patients are recommended to adhere to low-fat dietary guidelines. It is clear that the food and fat effects seen with most, if not all, currently marketed fenofibrate formulations may lead to unpredictable, inconsistent and non-optimal bioavailability especially when switching patients from one fenofibrate formulation to another. Consequently, in our opinion it would be necessary to systematically carry out the bioequivalence studies on fenofibrate formulations under high-fat fed conditions, which represent the "worst-case scenario".

In conclusion, the results of this bioequivalence study show that, under high-fat fed conditions, the 200 mg fenofibrate Lidose hard capsules are suprabioavailable (the GMR for AUC is 1.37) compared to the 145 mg fenofibrate nanoparticle tablet. It would be interesting to assess how this difference in fenofibric acid exposure affects the patient's triglyceride levels.

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