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RESEARCH

Further elucidation on the effect of food on the pharmacokinetics of trientine

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Abstract

Purpose Trientine dihydrochloride (TETA-2HCl) – a copper-selective chelator that forms a stable soluble complex with copper (Cu) and promotes excretion of this complex via the urine – is used as a treatment in Wilson Disease (WD) patients who are intolerant to D-penicillamine. Although in clinical practice patients are instructed to take TETA-2HCl on an empty stomach at least one hour before meals or two hours after meals, the effect of food on the pharmacokinetics of TETA-2HCl has not previously been systematically investigated in humans.

Methods In this open-label, single dose, randomized, two period cross-over study in healthy adults, a single oral dose of 600 mg of TETA-2HCl (2 × 300 mg capsules) was once administered under fed and once under fasted conditions with a wash-out period of at least one week. Blood samples were collected for up to 48 h after each dosing for analysis of plasma trientine (TETA) and its metabolites N1-acetyltriethylenetetramine (MAT) and N1-N10-diacetyltriethylenetetramine (DAT).

Results Food had a significant effect on the pharmacokinetics of TETA and its metabolites MAT and DAT. Maximum plasma concentrations, and the exposures of TETA are significantly reduced by food (C_{max}: 45%, AUC_{0-t} and AUC_{0-inf}: 44%.). Similar effects were seen for the metabolites MAT and DAT. The tolerability of treatment with TETA-2HCl was not affected by the intake of food.

Conclusion The study shows a significant impact of food on the pharmacokinetics of TETA, supporting the current instruction on administration of TETA-2HCl on an empty stomach in clinical practice.

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Keywords Wilson disease · Trientine dihydrochloride · Food · Pharmacokinetics

Introduction

Wilson disease (WD) is a rare autosomal recessive disorder of copper (Cu) metabolism caused by mutations of the ATP7B gene leading to impaired biliary excretion of copper and thus to Cu accumulation in several organs. Toxic Cu levels may result in a wide range of negative medical effects in patients, including hepatic, neurological, ophthalmic, and psychiatric manifestations. Treatment aims to remove excess Cu through facilitation of Cu excretion by binding excess copper in serum using chelating agents such as D-penicillamine and trientine (TETA) (trientine dihydrochloride [TETA-2HCl] as well as trientine tetrahydrochloride [TETA-4HCl]). The latter being a second line treatment for patients who do not tolerate D-penicillamine [1]. Although efficacy between both chelators is similar,

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TETA seems to be better tolerated in comparison to D-penicillamine [1, 2].

TETA-2HCl was first approved in the UK in 1985. During its initial use the effect of food on TETA's pharmacokinetics (PK) in humans had not yet been investigated. However, a 2–9-fold reduction in oral bioavailability had been observed in rats and dogs when TETA-2HCl was administered in the fed state as compared to the fasted state [3–6]. The reduced systemic exposure is likely to be due to the presence of TETA chelating copper in the gut contents, with the resulting TETA-Cu^{2+} complex having relatively poor absorption properties and largely being excreted in the faeces [7]. The increased concentration of physiological polyamines in the gastro-intestinal tract following a meal may also be a factor [8], supporting the idea that food intake might reduce the bioavailability of TETA [4, 9].

In humans, the absorption rate of TETA in the gut after oral trientine administration is known to be relatively slow, with maximum absorption reported after 0.8 to 4 h [10, 11]. However, the bioavailability of TETA, and any resulting impact on its efficacy and safety, in fed versus fasted states has not been investigated. Therefore, patients who are prescribed TETA-2HCl are advised to take the drug on an empty stomach (i.e., well before a meal or a couple of hours thereafter) in line with the available preclinical data [12].

This PK study aimed to assess the effect of food on the PK of TETA and its metabolites by administration of TETA-2HCl under both fed and fasted conditions.

Materials and methods

This was a Phase 1, single-dose, open label, randomized, two period cross-over, PK study in 24 healthy male and female subjects. The study was performed between July 11, 2018, and September 12, 2018, and was conducted by QPS-Netherlands in accordance with the principles of Good Clinical Practice (GCP) and the latest version of the Declaration of Helsinki as well as with all national and local laws of the appropriate regulatory authorities. The study and all related documents were approved by an independent ethics committee (St. BEBO, Assen, The Netherlands). All study participants signed an informed consent form before any screening activities commenced.

The primary objective of the study was to assess the effect of food on the PK of 600 mg (i.e., 2 × 300 mg capsules) of TETA-2HCl (300 mg dihydrochloride salt of TETA containing 200 mg of TETA base). The secondary objectives were to evaluate the PK of its metabolites (MAT and DAT) under fast and fed conditions, and to compare the tolerability of TETA after administration of TETA-2HCl capsules in fed and fasted conditions.

Study population and data collection

A total of 24 healthy subjects participated in the study. No formal statistical sample size calculations have been made, but the number of healthy subjects is based on previous experience and was considered to be adequate to address the study objectives [13–15].

Inclusion/exclusion criteria and restrictions prior and during the study period

The inclusion and exclusion criteria are summarized and presented in Supplementary Table 1. Briefly, healthy subjects were eligible for inclusion in the study if they were aged between 18 and 75 years, had a BMI between 18 and 30 kg/m^2, were able to provide informed consent to take part in the trial, had normal serum Cu and ceruloplasmin (Cp) levels, normal estimated glomerular filtration rate (eGFR), and did not have an abnormal diet, were not anemic, pregnant, planning to become pregnant, breastfeeding, using any prescription or over the counter medications, recent blood donors, or smoked more than 5 tobacco products per day.

All applicable acceptable forms of birth control for female and male subjects during the study are listed in the Supplement (Table S1).

Restrictions prior and during the study period

Subjects were restricted in the consumption of beverages and foods containing alcohol, grapefruit, or caffeine/xanthine; these were not allowed in each treatment period from 48 h prior to dosing until the last PK sample had been collected (day 3). However, allowance for an isolated single incidental consumption could be evaluated and approved by the investigator based on the potential for interaction with the study drug. Tobacco, nicotine products or e-cigarettes were not allowed during confinement in the clinical research facility. Subjects were not allowed to engage in strenuous exercise from 48 h prior to the first dose of study medication until the follow-up visit.

Treatments and assessments

Subjects received in a randomized order a single oral dose of 600 mg TETA-2HCl (Univar Solutions B.V., Rotterdam, the Netherlands) (2 × 300 mg capsules, equivalent to 2 × 200 mg TETA base) once under fasted conditions and once under fed conditions. The wash-out period between the successive doses was at least one week. Based on previous experience, a dose of 600 mg TETA-2HCl was considered to provide sufficient exposure in plasma to characterize the PK of TETA [13, 14].

The effect of food on the absorption of TETA was assessed with a high-fat, high-calorie (approximately 800–1000 kcal) meal as recommended by applicable guidelines for food effect studies [15]. This high-fat, high-calorie meal was expected to provide the greatest impact on gastrointestinal physiology – thereby maximally affecting the systemic drug availability.

The high-fat breakfast consisted of 2 large eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 125 g of hash brown potatoes and 250 mL of whole milk. Subjects fasted for 10-hours (overnight fast) before receiving the high-fat, high-calorie meal. Subjects had to complete this meal in 25 min or less as drug administration was performed 30 min after the start of the meal. The TETA-2HCl 300 mg capsules were administered orally with 240 mL of water and subjects fasted for an additional 4 h following drug administration. In subjects receiving TETA-2HCl under fasted conditions, the study medication was administered with 240 mL of water immediately after the 10-hour fast. Subjects then continued to fast for an additional 4 h.

Prior to each drug administration, vital signs, laboratory tests, drug screen, alcohol tests, and a pregnancy test (in urine) were performed, and the inclusion and exclusion criteria were reviewed. During each treatment period, blood samples of 2 mL for the PK analysis of TETA, MAT, and DAT in plasma were collected at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 20, 24, 30, 36, and 48 h post-dose. Blood was collected in K_2EDTA tubes, processed to plasma, and stored at -80 °C.

For each treatment period, subjects remained in the clinic from the afternoon before the study medication was administered until the morning of day 3, after the last PK sample (48 h) had been taken. During their stay in the clinical research facility, subjects received standardized meals and snacks around the same time each day except for the high-fat, high-calorie meal for the subjects who were being assessed in a fed state. Between 7 and 10 days after the last drug administration, subjects visited the clinical research facility for a follow-up visit. During the visit the following end-of-study procedures were performed including vital signs, 12-lead ECG, clinical laboratory parameters, pregnancy test for women (in urine), monitoring for adverse events (TEAEs) and concomitant medication.

Clinically relevant changes in vital signs, ECGs and laboratory parameters were reported as TEAEs.

Bioanalytical methods

Trientine and its metabolites MAT and DAT were analyzed by QPS Netherlands B.V., Groningen, the Netherlands, using a liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with TETA-d_4.4HCL, MAT-d_4.3HCL MAT-d_4.2HCL as internal standard. The assay was validated and sample analysis was conducted in accordance with Good Laboratory Practice principles [16]. The assay involved sample preparation by extraction of TETA, MAT and DAT from human K_2EDTA plasma via protein precipitation followed by derivatization with fluorenylmethyloxycarbonyl chloride. After quenching samples were analyzed using an API 400 LC-MS/MS system (Agilent). The range of quantification for all three analytes was 20–2000 ng/mL. Precision and accuracy was set to 15%, except for the lowest concentration of 20 ng/mL, precision and accuracy were set to 20%. Incurred sample re-analysis (ISR) was performed on 9% of samples with 20.0% assay variability in at least 2/3 of samples. Samples were stored at -80 °C for up to 45 days between sampling and bioanalysis, well within the confirmed long-term storage stability of 450 days at -80 °C.

Outcome measures for pharmacokinetics

Pharmacokinetic outcomes were measured by the calculation of the maximum plasma concentration (C_{max}) and related time (T_{max}), area under the curve from time zero to the last measurable concentration (AUC_{0-t}), area under the plasma concentration from time zero to infinity (AUC_{0-inf}), the terminal elimination half-life, and the terminal elimination rate constant for TETA, MAT and DAT.

Statistical analysis was performed on C_{max}, AUC_{0-t}, and AUC_{0-inf} of both treatments (fasted and fed). The primary PK parameters underwent logarithmic transformation and were analyzed using a mixed effects model including terms for treatment, period and sequence as fixed effects and subject within sequence as a random effect. The PK parameters of TETA and its metabolites were derived from individual subject plasma concentration time data using a non-compartmental method and are listed and summarized by treatment using descriptive statistics.

The ratios of the geometric means of TETA and its metabolites under fed/fasted conditions and 90% confidence intervals (CI) were calculated to determine the food effect. Bioequivalence was concluded when the 90% confidence ranges fell within the 80–125% range. Pharmacokinetic parameters were calculated for each treatment by non-compartmental methods using Phoenix WinNonlin, version 6.3 (Certara, Princeton, NJ, USA). Actual elapsed blood sampling times were used for the estimation of the PK parameters and descriptive presentations were provided by treatment group and nominal times.

Outcome measures of tolerability

For safety outcomes, treatment-emergent adverse events (TEAEs) recorded during the study were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 21.0). All TEAEs were summarized in its totality and by both fasted and fed treatment, by relationship, and by severity.

Results

Study population

Overall subject demographics and baseline characteristics are summarized and presented in Table 1.

Of the 24 randomized subjects, 23 subjects completed the study. One subject did not complete the study based on the subjects' own decision. This subject discontinued treatment on day 1, 5 h after receiving a single oral dose of 600 mg TETA-2HCl under fed conditions. One subject used concomitant medication: the subject used paracetamol for menstrual pain on day 2 after receiving a single oral dose of 600 mg of TETA-2HCl under fed conditions. This concomitant medication used during the study was considered not to have had any effect on the safety and PK parameters. All subjects were included in the PK analysis, and tolerability evaluations.

Table 1 Demographics and baseline characteristics

	All subjects*(N=24)
Age (years)	
n	24
Mean (SD)	45.2 (18.39)
Median (min, max)	51.5 (18, 73)
Sex	
Female	17 (70.83%)
Male	7 (29.17%)
Ethnicity	
Non-Hispanic/Non-Latino	24 (100%)
Race	
White	23 (95.83%)
Other	1 (4.17%)
Height (cm)	
n	24
Mean (SD)	172.27 (8.485)
Median (min, max)	174.20 (157.4, 187)
Weight (kg)	
n	24
Mean (SD)	73.77 (9.857)
Median (min, max)	73.80 (52.3, 92.5)
BMI (kg/m^2)	
n	24
Mean (SD)	24.82 (2.437)
Median (min, max)	24.95 (19.5, 29.2)

*BMI,*body mass index; *SD,* standard deviation

*All subjects participated in both assessments, i.e., having TETA-2HCl administered under fed and fasted conditions

Pharmacokinetic outcomes

TETA, MAT and DAT plasma concentration profiles obtained after dosing in the absence and presence of food are shown in Fig. 1. The summary of PK parameters is presented in Table 2 and the statistical treatment comparisons of the plasma PK parameters for TETA, MAT and DAT are presented in Table 3.

The first quantifiable TETA plasma concentrations were observed at 0.5 h post-dose in most subjects, both under fed and fasted conditions. Plasma concentrations further increased reaching a median T_{max} at 2 h under fasted conditions and 4 h after fed conditions, suggesting a prolongation of the absorption phase by 2 h due to food intake. Mean values of TETA C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 578 ng/mL, 2720 ng*h/mL, and 2940 ng*h/mL under fed conditions, compared to 1090 ng/mL, 5000 ng*h/mL, and 5170 ng*h/mL, respectively, under fasted conditions. Overall, under fed conditions the mean PK values (TETA C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) were 33–47% lower than under fasted conditions. The 90% CI of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of TETA were all outside the pre-specified range of 80–125%, indicating a significant effect of food.

Also, the apparent terminal elimination half-life under fasted conditions was slightly higher than under fed conditions (4.42 h versus 2.94 h). Between-subject variability (%CV) tended to decrease when TETA-2HCl was administered with food, since the CVs of AUC_{0-t}, $AUC_{0-\infty}$ and $t_{1/2}$ under fasted conditions were 61%, 61% and 108% compared to 50%, 48% and 72%, respectively, under fed conditions.

The appearance phase for MAT in the circulation was similar in both the fed and fasted states (median T_{max} 6 h versus 5.5 h), whereas prolongation of the appearance phase by 2 h under fed conditions was observed for DAT (median T_{max} 8 h versus 6 h in the fed and fasted states, respectively).

For MAT, mean values of C_{max} and $AUC_{0-\infty}$ were 965 ng/mL and 10,600 ng*h/mL under fed conditions, compared to 1350 ng/mL and 14,000 ng*h/mL, respectively, under fasted conditions. Based on the geometric least square mean (GLSM, Table 3) the values for C_{max} and AUC_{0-inf} were under fed conditions 30% and 25% lower than under fasted conditions, respectively. The 90% CI of C_{max} and $AUC_{0-\infty}$ of MAT were all outside the pre-specified range of 80–125%, indicating a significant food effect (Table 3).

Overall, similar effects of food were seen on the PK of DAT with mean values of C_{max} and $AUC_{0-\infty}$ of 232 ng/mL

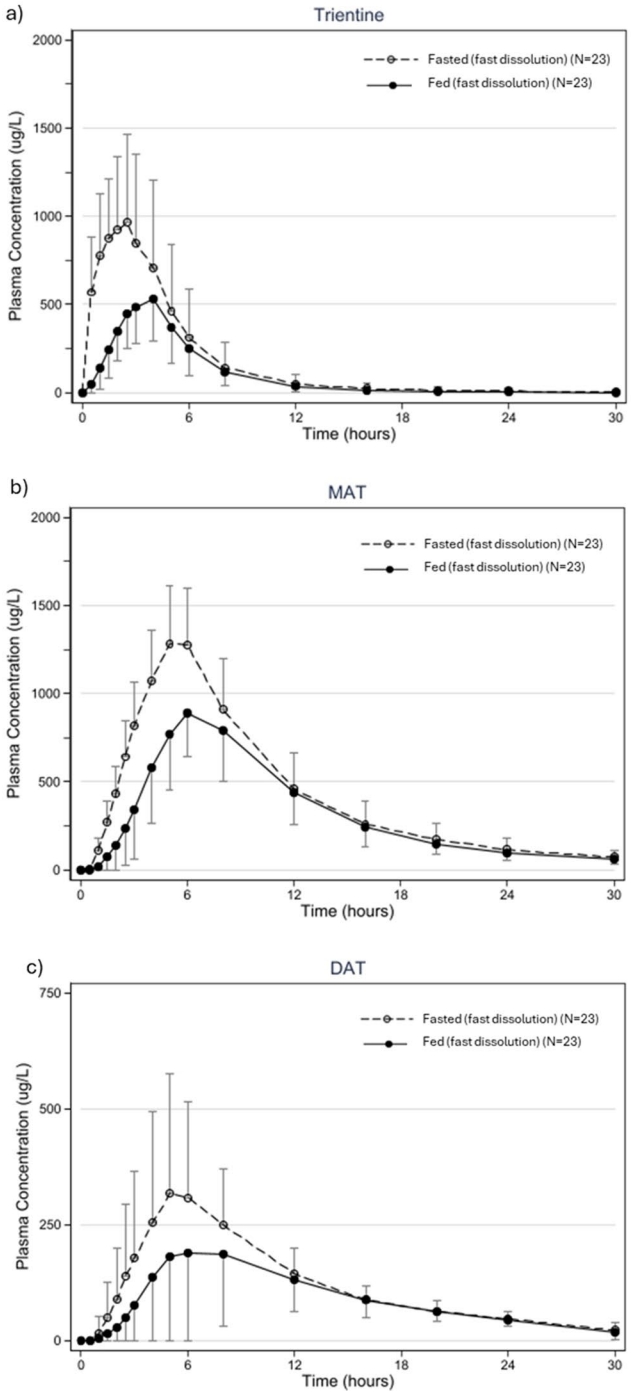

Fig. 1 Mean (SD) Plasma Concentration-Time Profiles after Administration of TETA-2HCl under fed and fasted conditions for **a**) TETA, **b**) MAT, and **c**) DAT

and 3430 ng*h/mL respectively under fed conditions, compared to 327 ng/mL and 3850 ng*h/mL, respectively, under fasted conditions. Based on the GLSM (Table 3) the values for C_{max} and AUC_{0-inf} were under fed conditions 42% and 24% lower than under fasted conditions, respectively. The

Table 2 Summary of TETA, MAT and DAT Pharmacokinetic parameters after administration of TETA-2HCl under fed and fasted conditions

	Fasted conditions		Fed conditions	
Parameters	*N*	Mean (SD) (CV%)	*N*	Mean (SD) (CV%)
TETA				
C_{max}[a] (ng/mL)	24	1090 (551) (50.3)	23	578 (238) (41.2)
T_{max}[a, b] (hr)	24	2.0 (0.5, 6.1) (53.8)	23	4.0 (2.0) (5.0) (18.6)
AUC_{0-t}[a] (ng*h/mL)	24	5000 (3050) (61.1)	23	2720 (1370) (50.4)
AUC_{0-inf}[a, c] (ng*h/mL)	24	5170 (3140) (60.7)	22	2940 (1400) (47.5)
$t_{1/2}$[a, c] (hr)	24	4.42 (4.76) (107.7)	22	2.94 (2.11) (71.8)
MAT				
C_{max}[a] (ng/mL)	24	1350 (321) (23.8)	23	965 (331) (34.3)
T_{max}[a, b] (hr)	24	5.5 (4.0, 6.1) (12.1)	23	6.00 (5.0) (8.0) (15.2)
AUC_{0-t}[a] (ng*h/mL)	24	13,300 (3970) (29.9)	23	10,000 (2940) (29.3)
AUC_{0-inf}[a] (ng*h/mL)	24	14,000 (4230) (30.1)	23	10,600 (3070) (28.9)
$t_{1/2}$[a] (hr)	24	14.1 (3.74) (26.5)	23	12.8 (12.8) (32.0)
DAT				
C_{max}[a] (ng/mL)	24	327 (255) (78.1)	23	232 (283) (121.9)
T_{max}[a, b] (hr)	24	6.0 (5.0, 8.0) (16.1)	23	8.0 (8.0) (12.0) (28.5)
AUC_{0-t}[a] (ng*h/mL)	24	3540 (1850) (52.3)	23	2640 (1870) (71.0)
AUC_{0-inf}[a] (ng*h/mL)	24	3850 (1880) (48.7)	17[c]	3430 (1930) (56.1)
$t_{1/2}$[a] (hr)	24	8.46 (3.01) (35.6)	17[c]	7.72 (1.27) (16.5)

GLSM, Geometric least squares

[a]Pharmacokinetic parameters for one subject receiving TETA-2HCl under fed conditions could not be estimated due to insufficient data

[b]Median (min, max) is presented

[c]AUC0-inf is not reportable for six subjects of treatment B due to percentage of extrapolated AUC > 20%

90% CI of C_{max} and $AUC_{0-\infty}$ of DAT were also all outside the pre-specified range of 80–125%, indicating a significant food effect (Table 3).

Tolerability results

There were no deaths, serious adverse events (SAEs), TEAEs leading to discontinuation, or other medically

Table 3 Statistical comparisons of plasma Pharmacokinetic parameters

	Fasted (N=24)	Fed (N=23[a])	Fasted vs. fed condition
	GLSM	GLSM	GMR (90% CI)
TETA			
C_{max} (ng/mL)*	968	528[a]	54.52 [47.73, 62.29]
AUC_{0-t} (ng*h/mL)*	4210	2370[a]	56.39 [48.43, 65.67]
AUC_{0-inf} (ng*h/mL)*	4360	2440[a]	56.01 [48.50, 64.69]
MAT			
C_{max} (ng/mL)*	1310	909[a]	69.64 [61.91, 78.33]
AUC_{0-t} (ng*h/mL)*	12,600	9500[a]	75.21 [67.61, 83.65]
AUC_{0-inf} (ng*h/mL)*	13,400	10,100[a]	75.37 [67.91, 83.64]
DAT			
C_{max} (ng/mL)*	275	159[a]	57.73 [51.36, 64.89]
AUC_{0-t} (ng*h/mL)*	3160	2130[a]	67.38 [60.67, 74.82]
AUC_{0-inf} (ng*h/mL)*	3480	2630[a, b]	75.56 [68.84, 82.94]

GLSM, Geometric least squares mean; *GMR*, Geometric Mean Ratios

*Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values

[a]C_{max}, AUC_{0-t} and AUC_{0-inf} could not be estimated for one subject due to insufficient data

[b]AUC0-inf is not reportable for six subjects of treatment B and for one subject of treatment C due to percentage ofextrapolated AUC > 20%

important adverse events reported in this study (Table S3). Out of the 24 subjects, 9 [37.5%] reported a total of 14 TEAEs in the fasted group and 6 subjects [25%] reported 5 TEAEs in the fed group. (Table S4). Headache and nausea were the most commonly reported TEAEs, all of which were considered mild. One participant (11.11%) experienced a TEAE (abdominal pain) of moderate intensity that was considered unrelated to the treatment after being administered TETA-2HCl under fasted conditions. Two participants who took TETA-2HCl under fasted conditions (22.22%) reported 3 TEAEs (nausea, feeling hot, and headache) that were considered related to the study drug, and 1 participant (16.67%) reported a TEAE (headache) after taking TETA-2HCl under fed conditions (Table S5). There were no clinically significant abnormal laboratory values or vital signs, or ECG findings in this study. Overall, there were no clinically significant differences in the tolerability profiles between treatments; TETA-2HCl was well-tolerated, with an acceptable tolerability profile under both fed and fasted conditions.

Discussion

This study shows that there is a clear effect of food on the PK of TETA and its metabolites in healthy subjects. Under fed conditions, exposure of TETA and its metabolites is reduced by 40–45% as compared to fasted conditions. Although preclinical data suggested food was likely to reduce bioavailability of TETA [3–6], this study is the first to investigate the food effect on TETA PK in humans, since trientine dihydrochloride became available in the UK in 1985.

TETA plasma concentrations reached T_{max} at 2 h under fasted conditions and 4 h after fed conditions, suggesting a prolongation of the absorption phase by 2 h. A similar effect was also observed for DAT, with a T_{max} of 6 h and 8 h under fasted and fed conditions, respectively. For MAT, the prolongation of the formation and appearance phase in the circulation was less obvious, T_{max} under fasted and fed conditions was 5.5 h and 6 h, respectively. These results are similar to those reported in preclinical studies, where, although bioavailability differed substantially between studies, food intake was generally reported to lower bioavailability of oral TETA [10].

The apparent terminal elimination half-life of TETA under fed conditions was also slightly higher than under fasted conditions. As expected, the apparent terminal elimination half-life for both MAT and DAT did not differ substantially when TETA-2HCl was administered under fed and fasted conditions. Between-subject variability for the PK parameters C_{max} and $AUC_{0-\infty}$ for MAT and DAT under fed and fasted conditions were slightly mixed: MAT variability for C_{max} was higher with food but was similar for $AUC_{0-\infty}$ values under fed and fasted conditions, whereas DAT variability on C_{max} and $AUC_{0-\infty}$ was highest under fed conditions. These results further emphasize the effect food has on the PK parameters after trientine dihydrochloride administration.

Adherence to treatment regimens can be impacted by various factors like the time of medication intake, dosage form, and the frequency of medication use [17–19]. It is therefore important that dosing instructions are simplified wherever possible, and that restrictions such as the requirement to take the medication on an empty stomach are only included if demonstrated to be clinically necessary. A study by Maselbas et al. (2010) found that up to 25% of patients with WD were not consistent in taking their prescribed WD medication which reflected negatively on their chances for improvement and was also considered to be causing clinical deterioration [20]. Recently, low medication compliance was found in 32% of WD patients [17], meaning it is of particular importance to ascertain whether the current dosing requirements for TETA-2HCl are necessary, both for efficacy and tolerability.

The results of this study emphasize the importance of the instruction given to WD patients to take TETA-2HCl on an empty stomach, at least one hour before a meal or two hours after a meal as the effect on the level of drug absorption may ultimately impact the efficacy of treatment with TETA-2HCl. It is important that patients are aware of the necessity to adhere to the instructions regarding administration, and that poor compliance regarding dosing instructions may result in an inadequate therapeutic effect, ultimately leading to early neurological symptoms or liver failure. Importantly, this is not only expected if doses are missed, but also if TETA-2HCl is not taken on an empty stomach, as emphasized by the results of this study.

A reduced bioavailability has also been shown in healthy subjects for D-penicillamine [21]. Schuna et al. (1983) showed that in fasted individuals the bioavailability was reduced by half. Together with this previous observation, our data might not only emphasize the importance of administration of TETA-2HCl on an empty stomach, but the importance of administration on an empty stomach for all chelators used in the treatment of Wilson disease. Regarding Wilson disease treatment with Zinc, administration on an empty stomach is also recommended [22], as it is assumed that concomitant intake of food would reduce the absorption of Zinc.

This study not only aimed to assess the effect of food on the PK of TETA but also to assess and compare the tolerability after administration of TETA-2HCl capsules in fed and fasted conditions.

Taking into account the limited number of reported TEAEs in this small sample size study, there are no indications that the observed differences in the PK of TETA and its metabolites in fed and fasted states affect the tolerability profile of TETA-2HCl. The most frequently reported TEAEs were nausea and headache. No significant differences/new safety signals were observed.

The main limitation of the study is that it was not conducted in WD patients, but in healthy subjects, as per FDA/EMA guidance on food effect studies. Indeed, healthy subjects do have an undisturbed Cu homeostasis. Therefore, verifying the study results in WD patients will be important. Furthermore, the study was conducted as a within-subject comparison, therefore apart from the fasting/non-fasting conditions, all experimental conditions were similar during both periods. Other studies have shown similar PK profiles of TETA between patients with WD and healthy subjects [13]. Therefore, it is very unlikely that the current study results are dependent on the study population. Additionally, although study subjects received the guideline-recommended high fat, high calorie meal for the fed state, the meal was not chosen based on its copper content so a high Cu meal may have further impacted TETA-2HCl absorption. Further, this study had a limited sample size. However, the number of 24 healthy subjects was considered to be adequate to assess the effect of food on the PK of TETA and to compare the tolerability after administration of TETA-2HCl capsules in fed and fasted conditions. In addition, WD is a rare disease and exposure to TETA is in line with that and therefore it can be expected to see similar results in clinical practice.

Overall, this study showed that food has a significant effect on the PK of TETA and its metabolites, MAT and DAT maximum plasma concentrations and exposures were significantly reduced by food. There was no indication that the tolerability profile of TETA-2HCl is affected by the simultaneous intake of food. This study emphasizes that the advised method of administration of taking TETA-2HCl on an empty stomach is important to ensure systemic exposure, while taking TETA-2HCl with food shows a significant reduction in absorption.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-025-03953-0.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests K.H. Weiss advises for Univar Solutions BV, Vivet Therapeutics, Alexion, Orphalan, Ultragenyx, Pfizer, AbbVie, Bayer and is on the speakers bureau of Alexion, Orphalan and Falk and received travel support from Alexion. For the remaining authors, no conflict of interests were declared.

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