A study to determine the potential effects of dissolution rate and food on the pharmacokinetics of trientine dihydrochloride following single oral administrations in healthy subjects

Peter Dogterom[1], Mireille Gerrits[2], Khalid Abd-Elaziz[1], Daphne van Scheppingen[3], Carlot Kruse[3]

1. QPS Netherlands, Groningen, The Netherlands
2. In2Clinic, Wageningen, The Netherlands
3. Univar Solutions B.V., Rotterdam, The Netherlands

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INTRODUCTION

Trientine dihydrochloride (trientine) is a well-established treatment for Wilson Disease patients intolerant to D-Penicillamine. However, data on the pharmacokinetics (PK) of trientine is limited.

AIM

1. To investigate the PK of trientine with two different *in-vitro* dissolution rate profiles

2. To investigate the effect of food on the PK of trientine.

In addition, the PK of the main metabolites of trientine, N_1-acetyltriethylenetetramine (MAT) and N_1,N_{10}-diacetyltriethylenetetramine (DAT) were investigated.

MATERIAL & METHODS

This was a randomized, three-way crossover, open-label study. Twenty-four healthy male (7) and female (17) volunteers, aged 18 to 75 years, received three separate single oral doses of 600 mg trientine (two 300 mg capsules) as:

- Treatment A: capsules with a fast dissolution profile under fasted conditions (10 hours overnight fast).
- Treatment B: capsules with a fast dissolution profile under fed conditions (high-fat, high-calorie breakfast 30 minutes prior to drug administration).
- Treatment C: capsules with a slow dissolution profile under fasted conditions (10 hours overnight fast).

Each period, blood samples for the bioanalysis of trientine and its metabolites were collected up till 48 hours after dosing. All compounds were analyzed by LC-MS/MS.

Treatment comparisons were performed on the log-transformed pharmacokinetic parameters maximum plasma concentration (C_{max}), area under the plasma concentration versus time curve to the last measurable concentration (AUC_{0-t}) and to infinity (AUC_{0-inf}). The time to reach the maximum plasma concentration (T_{max}) and the elimination half-life ($t_{1/2}$) were summarized descriptively, without formal statistical comparison.

RESULTS

- The plasma profiles and derived primary PK parameters (i.e. C_{max}, AUC_{0-t}, AUC_{0-inf}) of trientine after the intake of capsules with a fast and a slow dissolution profile were comparable, although the AUC was slightly lower for the fast dissolution formulation (AUC_{0-t}: 8%, AUC_{0-inf}: 9%). The pharmacokinetics of MAT and DAT were comparable between the two formulations as well (Figures 1, 2 and 3).
- Food delayed the time to the T_{max} of trientine from 1.9 to 3.6 hours, whereas C_{max}, AUC_{0-t} and AUC_{0-inf} were decreased by approximately 45%, 44% and 44% respectively. For MAT and DAT, the T_{max} was delayed by 0.5 and 2 hours respectively and C_{max}, AUC_{0-t} and AUC_{0-inf} decreased by approximately 30%, 25% and 25% (MAT) and 42%, 33% and 24% (DAT) respectively.
- The 90% CI of C_{max} of trientine was within the bio-equivalance range of 80-125%. For the AUC_{0-t} and AUC_{0-inf}, the 90% CIs included 100%, but due to the large variation the 90% CIs of trientine were wide and the lower ends were slightly outside the range of 80-125%. Based on these results, bioequivalence between the slow and fast dissolution formulation cannot be claimed. However the treatment differences were small, and were therefore not considered to be of clinical relevance (Table 1).

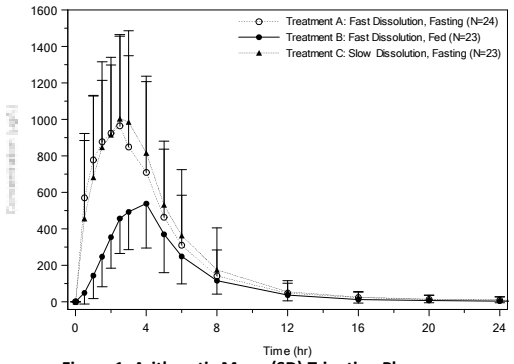

Figure 1: Arithmetic Mean (SD) Trientine Plasma Concentration-Time Profiles

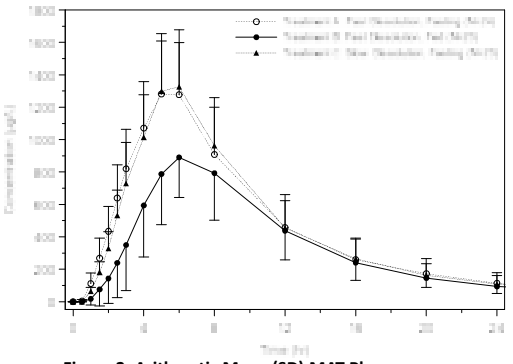

Figure 2: Arithmetic Mean (SD) MAT Plasma Concentration-Time Profiles

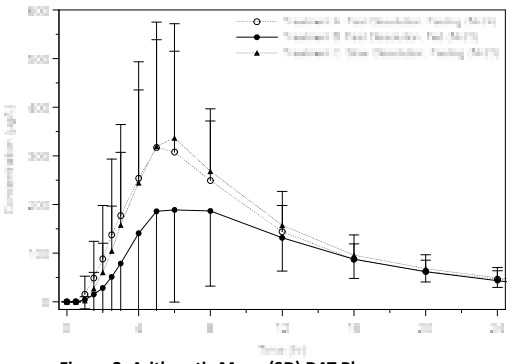

Figure 3: Arithmetic Mean (SD) DAT Plasma Concentration-Time Profiles

Table 1: An overview of the statistical comparisons of PK parameters of trientine

	Treatment A		Treatment B		Treatment C		Treatment A vs. C (dissolution rate)	Treatment B vs. A (food effect)
	N	GLSM	N	GLSM	N	GLSM	GMR (90% CI)	GMR (90% CI)
C_{max}[a] (ng/mL)	24	968	23[b]	539	23[b]	994	95.81 [83.87,109.46]	54.52 [47.73,62.29]
AUC_{0-t}[a] (ng*h/mL)	24	4210	23[b]	2370	23[b]	4580	91.90 [78.96,107.07]	56.39 [48.43,65.67]
$AUC_{0-\infty}$[a] (ng*h/mL)	24	4360	22	2680	21	4940	90.65 [78.32,104.91]	56.01 [48.50,64.69]
T_{max} (h)	24	1.92	23	3.62	23	1.99	Not done	Not done
$t_{1/2}$ (h)	24	3.2	22	2.49	21	3.30	Not done	Not done

[a]Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values
CI=Confidence interval; GLSM=Geometric least squares mean; GMR=Geometric least squares mean ratio between treatments; N= Number of subjects; GMR and 90% CI are reported as percentage
[b]Twenty-three (23) subjects completed the study. One (1) subject did not complete the study (subject's decision)

CONCLUSION

- **The PK and safety evaluation demonstrate that the 300 mg trientine capsule with the fast dissolution rate is comparable to the 300 mg trientine capsule with the slow dissolution rate.**
- **The intake of food within 30 minutes prior to trientine administration delays the absorption and reduces the exposure to trientine by approximately 44%.**
- **No differences in safety and tolerability were observed between trientine capsules with a fast and slow dissolution rate, or between administration of the trientine capsules with a fast dissolution rate in the fed and fasted condition.**

DISCLOSURES

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CONTACT INFORMATION

Peter Dogterom; peter.dogterom@qps.com