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Wilson's disease

Specific pharmacokinetic features of two trientine preparations and their potential impact on treatment outcome

Kilian Weigand[1], Alberto Corsini[2]

[1] Department of Gastroenterology and Gastrointestinal Oncology, Gemeinschaftsklinikum Mittelrhein, Koblenz, Germany

[2] Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Milano, Italy

SUMMARY

Wilson's disease (WD) is caused by a genetic defect in copper metabolism, which leads to toxic accumulation of copper, especially in the liver and brain. In the symptomatic stage, the oral copper chelating agents D-penicillamine and trientine are approved therapeutic agents. D-penicillamine is recommended by the guidelines as the first option. In case of severe side effects, which often occur with this therapy, treatment is switched to the better tolerated trientine. For all approved WD therapies, enteral absorption of the chelating agent is significantly reduced by food intake, so patients must follow strict meal spacing rules. In addition, because trientine must be taken in 2–4 divided doses distributed over the day, this can create organizational challenges and pose adherence problems for patients. However, there are pharmacokinetic differences between the two trientine preparations centrally authorised in the EU, Cuprior® (trientine tetrahydrochloride) and Cufence® (trientine dihydrochloride), which may be important in everyday practice. Whilst both trientine salts share the same mode of action, the tetrahydrochloride (trientine 4HCl) formulation has a faster dissolution rate and more efficient absorption compared with trientine 2HCl, resulting in a higher bioavailability. This in turn may reduce the total daily dose needed and thus the pill burden for the patient. As early as 30 minutes after ingestion of trientine 4HCl, 73% of maximum plasma levels are reached, compared with only 21% after ingestion of trientine 2HCl. This suggests that unplanned food intake before the recommended interval following ingestion of trientine may have a lower impact on drug exposure and thus the extent of copper elimination with trientine 4HCl compared with trientine 2HCl. In conclusion, drug dissolution, absorption and food effect on bioavailability should be taken into account to be able to opt for the more advantageous trientine formulation because serum concentrations of the active moiety ultimately influence potency and efficacy.

Keywords: Wilson's disease, D-penicillamine, trientine dihydrochloride, trientine tetrahydrochloride, pharmacokinetics, absorption, bioavailability, adherence, dietary restriction

Contents

1. INTRODUCTION

Wilson's disease (WD) is a rare hereditary disorder of hepatic copper metabolism with autosomal recessive inheritance. If untreated, toxic copper accumulation occurs in various organs (*Mulligan & Bronstein, 2020*). The disease is caused by mutations in the *ATP7B* gene, which encodes a transmembrane copper transporter, a P-type ATPase (*Chang & Hahn, 2017*). ATP7B is involved in copper incorporation into the transport protein coeruloplasmin on the one hand, and in the excretion of copper into bile on the other. The reduced efficacy of these two mechanisms lead to copper accumulation and the progressive course of WD when ATP7B is defective (*Chang & Hahn, 2017*). Estimates for the prevalence of WD range from 1:30,000 to 1:50,000 (*Sandahl et al., 2020*). However, according to recent genetic studies using next generation sequencing, the frequency of genetic WD may be significantly higher, up to 15.4 cases per 100,000 newborns (*Gao et al., 2019*). The disease becomes clinically manifest mostly in childhood, adolescence, and early adulthood, but occasionally much later (*Mulligan & Bronstein, 2020*).

The accumulation of copper – mainly in the liver, but also in the kidney, placenta, mammary gland, cornea (Kayser-Fleischer ring), brain, and lungs – can be associated with a variety of severe clinical manifestations if left untreated, such as neurological symptoms (typically dystonia), hepatic insufficiency up to acute liver failure, psychiatric disorders (e.g., depression), and others. It is this clinical variability and the very heterogeneous age of manifestation, combined with the rarity of the disease, that often leads to delayed diagnosis and treatment for many years. If left untreated, Wilson's disease can be fatal. With adequate therapy, liver function stabilizes in most patients, and even severe neurological symptoms can regress, and affected individuals can return to a normal life (*Aggarwal & Bhatt, 2018*).

Fact Box Wilson's Disease

- WD is caused by a congenital mutation of a gene encoding the copper transporter ATP7B. Its malfunction leads to an accumulation of copper in the body.
- The disease can present with a variety of clinical manifestations beginning in childhood, including liver dysfunction, neurological symptoms, and psychiatric disorders.
- Given the wide variety of signs and symptoms, the diagnosis is often made late.

2. TREATMENT RECOMMENDATIONS FOR WILSON'S DISEASE

The goal of drug therapy for WD is to achieve and maintain normal copper homeostasis as early as possible in the course of the disease (*S1-Leitlinie, 2012*). Initially, a negative copper balance is intended to eliminate excess copper from the tissues. Subsequent lifelong maintenance therapy should maintain a normal copper balance. Currently, the copper chelating agents D-penicillamine (*Walshe, 1956*) and trientine (*Walshe, 1982*) and zinc salts (*Hoogenraad et al., 1979*) are available for WD therapy. While the chelating agents rapidly mobilize and renally eliminate the copper depot by forming a copper chelate complex, zinc induces the synthesis of metallothioneine in enterocytes. This protein binds copper which is subsequently excreted in the faeces, thus preventing copper absorption (*S1-Leitlinie, 2012*).

For symptomatic patients, German and international guidelines recommend treatment with D-penicillamine or trientine (*S1-Leitlinie, 2012; EASL, 2012; Palumbo u. Schilsky, 2019*). Treatment should be started with low doses with careful upward

Fact Box Treatment Recommendations

- WD is readily treatable by pharmacological inhibition of absorption and of elimination of excess copper from the body.
- With early initiation of therapy, affected individuals have a good prognosis.
- Available drugs include the copper chelators D-penicillamine and trientine with a dual mechanism of action (systemic chelation and inhibition of gastrointestinal absorption), and the absorption inhibitor zinc.

titration to prevent paradoxical worsening of neurological symptoms due to excessive copper mobilization (*S1-Leitlinie, 2012*). Some presymptomatic patients can be treated with zinc salts from the beginning to prevent the clinical onset of the disease (*S1-Leitlinie, 2012*). Overall, clinical evidence for current treatment recommendations is limited (*Appenzeller-Herzog et al., 2019; Palumbo & Schilsky, 2019*).

3. TRIENTINE – SECOND-LINE THERAPY AFTER D-PENICILLAMINE INTOLERANCE

In addition to D-penicillamine (*Metalcaptase®*), the two trientine preparations trientine dihydrochloride (trientine 2HCl, Cufence®) and trientine tetrahydrochloride (trientine 4HCl, Cuprior®) are available as oral copper chelators for the treatment of WD. Trientine is approved for patients 5 years of age and older who are intolerant to D-penicillamine (*Cufence® Fachinformation, 2021; Cuprior® Fachinformation, 2020*). Immediate discontinuation of D-penicillamine and switch to trientine is indicated if severe adverse events occur with D-penicillamine, such as renal impairment with creatinine increase and proteinuria, marked blood count changes (leukopenia, thrombocytopenia), skin changes, eye muscle paralysis, increase in ANA titers, or biochemical signs of liver toxicity with cholestasis and transaminase increase (*Metalcaptase® Fachinformation, 2014*). There are many additional side effects including gastrointestinal disorders, etc. Trientine has shown significantly fewer side effects compared with D-penicillamine in a retrospective study (*Weiss et al., 2013*).

4. PHARMACOKINETICS OF TRIENTINE

The dosage of copper chelators must be adjusted to the clinical response. Moreover, the total dose of trientine must be taken in 2–4 doses distributed over the day, with minimum time intervals to be observed between each drug intake and meals in order to prevent impaired enteral absorption and chelation of dietary metals in the intestinal tract. This is because both trientine formulations have a low bioavailability, and the extent of copper excretion is directly correlated with the plasma concentration of the trientine base (*Cho et al., 2009*). Both trientine preparations should therefore be taken at least one hour before or two hours after meals (*Cufence® Fachinformation, 2021; Cuprior® Fachinformation, 2020*). Of note, however, there are pharmacokinetic differences between trientine 2HCl and trientine 4HCl, which may be clinically important and will be discussed in more detail below due to a potential practical advantage for trientine 4HCl.

Fact Box Copper Chelators

- Guidelines recommend D-penicillamine as initial option for the treatment of symptomatic WD.
- If intolerance to D-penicillamine occurs, treatment should be switched to a trientine preparation.

4.1 Influence of food on the absorption of trientine 2HCl

An open-label randomized crossover study in 24 healthy volunteers (7 men and 17 women aged 18–75 years) investigated the influence of food intake on the pharmacokinetics of trientine 2HCl and its major metabolites N1-acetyltriethylenetetramine (MAT) and N1,N10-diacetyltriethylenetetramine (DAT) (*Dogterom et al., 2019*). In each of the three study arms, repeated plasma level measurements were made for 48 hours following a single dose of 600 mg trientine base (2 capsules of 300 mg). Two different formulations (capsules with fast and slow dissolution, respectively) were used, with the fast-dissolution capsules administered both in a fasting state and 30 minutes after a high-fat, high-calorie breakfast.

Fact Box Pharmacokinetic Profile of Trientine

- **Absorption:** Trientine is poorly absorbed from the intestine (6 %–18 % of oral doses), with high interpatient variability.
- **Distribution:** Little is known about distribution of trientine in organs and tissues. The drug is poorly bound to plasma proteins.
- **Biotransformation:** Trientine is acetylated to form two major metabolites, N1-acetyltriethylenetetramine (MAT) and N1,N10-diacetyltriethylenetetramine (DAT). MAT may also contribute to the overall clinical effect.
- **Elimination:** Trientine and its metabolites are rapidly excreted in the urine.

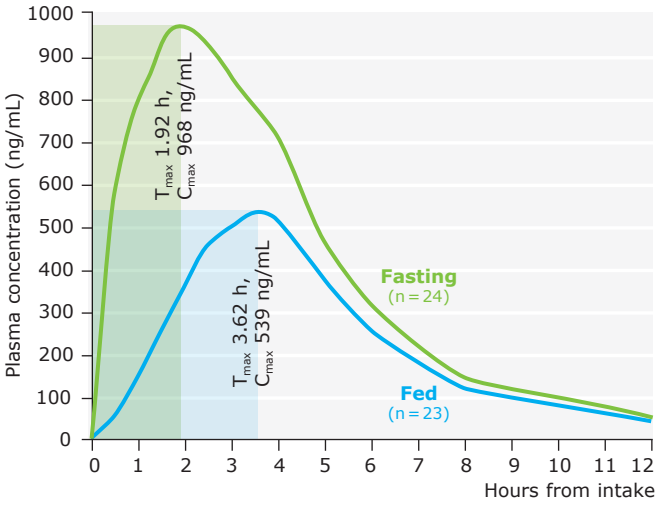

Figure 1. Mean plasma concentrations after a single dose of a trientine 2HCl formulation (corresponding to 600 mg trientine base) administered to healthy volunteers in the fasting state or 30 minutes after a meal (modified after *Dogterom et al., 2019*)

It was found that in the fasting state, pharmacokinetic differences between the slow and fast dissolution capsules were small, though interindividual variation was large. The pharmacokinetics of the metabolites MAT and DAT were also comparable with both formulations, suggesting no advantage in bioavailability with the fast dissolution.

In contrast, the influence of food intake on the pharmacokinetics of trientine 2HCl, using the fast dissolution capsules, was profound. A preceding meal reduced absorption and prolonged T_{max}, the time to reach the maximum plasma concentration C_{max}, from 1.9 to 3.6 hours in the fasting state. At the same time, C_{max} and total drug exposure ($AUC_{0-\infty}$) decreased significantly by 45 % and 44 %, respectively (Figure 1). Pharmacokinetic parameters for both metabolites MAT and DAT changed in the same direction. These results underscore the importance of keeping adequate distance to meals to ensure effective systemic trientine exposure for safe therapeutic copper elimination.

4.2. The TRIUMPH pharmacokinetic study: trientine 2HCl vs. trientine 4HCl

4.2.1 Study design

In TRIUMPH, a randomized phase I study with crossover design, the pharmacokinetics of the two commercially available trientine preparations (containing trientine 2HCl and trientine 4HCl, respectively) were compared after a single dose corresponding to 600 mg trientine base in 23 healthy adult volunteers in the fasting state (*Weiss et al., 2021*). Subjects received their assigned drug dose (3 capsules of 200 mg trientine 2HCl or 4 tablets of 150 mg trientine 4HCl) in the morning after 10 hours of fasting. After ingestion, subjects were not allowed to eat solid food for 4 hours (nor were they allowed to drink any liquid for 1 hour before and after ingestion). 8 days later, the subjects received the other drug.

In both study periods, blood samples were taken before the single dose and at close intervals thereafter (up to 48 hours) to measure the plasma concentrations of trientine and its metabolites MAT and DAT.

4.2.2 Results

Peak plasma concentrations of trientine were reached with trientine 4HCl after a median of 2 hours and with trientine 2HCl with one hour delay (a median of 3 hours). The peak drug concentration (C_{max}) and total systemic exposure ($AUC_{0-\infty}$) were approximately 68 % and 56 % higher, respectively, with trientine 4HCl compared with trientine 2HCl. The terminal elimination rate and half-life of trientine were similar with both preparations (Table 1). With respect to the two metabolites MAT

Fact Box Pharmacokinetics and Food Intake

- D-Penicillamine and trientine should be taken in the fasting state, with an appropriate interval from meals.
- The influence of food intake on the pharmacokinetics was specifically investigated with a trientine 2HCl formulation.
- A meal 30 minutes before oral intake of 600 mg trientine base delayed the rise in plasma levels, markedly reduced its absorption and thus also drug exposure.

Fact Box TRIUMPH Study Design

- TRIUMPH was a randomized crossover study to compare the pharmacokinetics of trientine 2HCl and trientine 4HCl in healthy, fasting subjects.
- After 10 hours of fasting, subjects received 600 mg of one drug (dose related to trientine base) followed by monitoring of plasma levels for 48 hours.
- 8 days later, the subjects were administered the other formulation at the same dose.

and DAT, the pharmacokinetic differences between the two formulations were smaller than with the parent compound trientine. The single doses of both trientine preparations were well tolerated by the subjects, and there were no safety problems.

The measured differences in the drug exposure of both formulations informed the posology of trientine 4HCl, confirming the dosage recommendations given in the corresponding Summaries of Product Characteristics. Accordingly, the dose of trientine 4HCl (Cuprior®) is only about 60 % of that of trientine 2HCl (Cufence®) (450 – 975 mg/day versus 800 – 1600 mg/day).

4.2.3 Plasma levels during the first hour

In a secondary analysis of the TRIUMPH 1 data, the pharmacokinetics during the first hour after oral administration of the two formulations at the same dose (600 mg trientine base) was examined to explore the potential impact of inadvertent food ingestion during this time interval.

The mean (SD) concentration of the trientine base at 30 and 60 mins was 1710 (1110) and 1762 (1161) ng/mL for trientine 4HCl, and 279 (227) and 589 (384) ng/mL for trientine 2HCl, respectively. The proportion of participants achieving C_{max} (**Figure 2**) at 30 and 60 minutes post ingestion was 32 % (8/25) and 48 % (12/25), respectively, for trientine 4HCl, while no subject reached the peak plasma level with trientine 2HCl.

These data suggest that the trientine 4HCl formulation has a very different early pharmacokinetic profile compared with trientine 2HCl in the first 30 and 60 minutes following ingestion, reflecting a 6 and 3 fold increase in absorption in favour of trientine 4HCl at these two timepoints. Any inadvertent food intake in the window of up to two hours after dosing is likely to impact the systemic absorption of the drug to a higher degree following trientine 2HCl administration compared with trientine 4HCl.

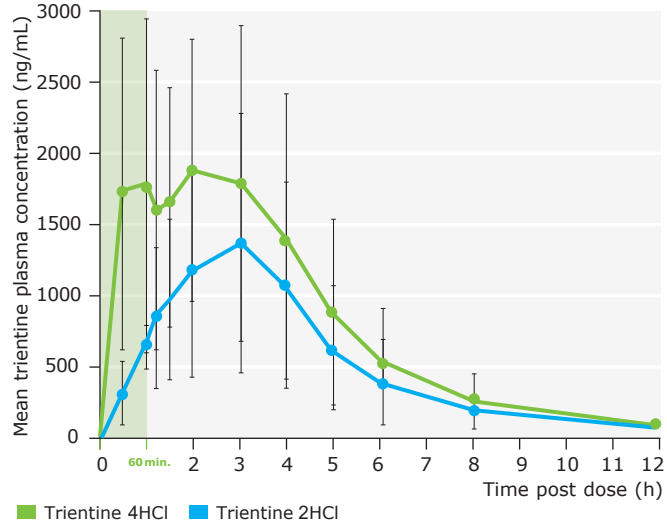

Figure 2. Plasma concentrations (mean ± standard deviation) after a single dose of trientine 4HCl and trientine 2HCl (600 mg trientine base each) to healthy volunteers in the fasting state (modified after *Weiss et al., 2021*)

5. DISCUSSION

Toxic accumulation of copper in WD is in principle easily treatable, so patients adherent to chelator therapy and dietary restriction can generally have a normal life expectancy (*EASL, 2012; Ala et al., 2007*). However, a prerequisite for this is, on the one hand, early diagnosis and treatment initiation with subsequent close monitoring of therapy, and on the other hand, patients' adherence to therapy (*Dziezyc et al., 2014; Palumbo & Schilsky, 2019*). These requirements are not easy to fulfill. The medical diagnosis of WD can be difficult, it is based on a

Table 1. Pharmacokinetics of trientine 4HCl and trientine 2HCl after a single oral dose corresponding to 600 mg trientine base (*Weiss et al., 2021*)

	Trientine 4HCl (n=23)	Trientine 2HCl (n=23)
	Mean ± SD (%CV)	Mean ± SD (%CV)
C_{max} , ng/mL	2340 ± 1170 (50.0)	1490 ± 864 (58.1)
T_{max} , median (range), h	2.00 (0.50-4.00)	3.00 (1.25–6.02)
AUC_{0-t} , ng·h/mL	10100 ± 5740 (57.0)	6600 ± 3870 (58.6)
$AUC_{0-\infty}$, ng·h/mL	10200 ± 5810 (56.7)	6790 ± 3950 (58.1)
λ_z, l/h	0.0590 ± 0.0952 (161.3)	0.0558 ± 0.0681 (122.1)
$t_{½}$, h	19.9 ± 8.70 (43.7)	23.2 ± 20.8 (89.9)

Abbreviations: SD = standard deviation, CV = between-subject coefficient of variation, C_{max} = maximum observed plasma concentration, T_{max} = time of maximum observed plasma concentration, AUC = area under the plasma concentration vs time curve from time zero to the last quantifiable time point (0 – t) and from time zero to infinity (0 – ∞), λ_z = rate of elimination for the terminal phase of the concentration-time curve, $t_{½}$ = terminal elimination half-life

Fact Box Pharmacokinetics of Trientine 2HCl vs. Trientine 4HCl

- C_{max} was reached after a median of 2 hours with trientine 4HCl and after 3 hours with trientine 2HCl.
- With trientine 4HCl, C_{max} was 68 % and $AUC_{0-\infty}$ 56 % higher compared with the same dose of trientine 2HCl.
- This difference in systemic exposure allows trientine 4HCl to be administered at a 40 % lower therapeutic dose than trientine 2HCl.
- The pharmacokinetic differences between the two trientine preparations were very pronounced within the first hour after ingestion.
- The greater proportion of subjects achieving C_{max} with trientine 4HCl in the first hour suggests that inadvertent food ingestion by patients is less likely to impact drug efficacy with trientine 4HCl compared with trientine 2HCl.

complex set of clinical findings derived from the patient's history and clinical examination, laboratory findings, and imaging (*Kasztelan-Szczerbinska & Cichoz-Lach, 2021*). Clinical and biochemical monitoring of treatment is demanding and must be performed regularly (*Palumbo & Schilsky, 2019; Weiss & Stremmel, 2014*). For the patients, consistent implementation and adherence to therapy is also a major challenge. For example, the tolerability of D-penicillamine is suboptimal, side effects are frequent and sometimes severe (*Kumar et al., 2021*). In such a case, it is necessary to switch to one of the two trientine preparations. Trientine, in turn, must be taken in 2–4 daily single doses, while simultaneously maintaining the minimal distances to food intake due to the strong food dependence of absorption (*Cho et al, 2009; Dogterom et al, 2019*). This is of critical importance for the outcome of therapy, as the efficiency of copper elimination depends directly on the plasma concentrations achieved (*Cho et al., 2009*). Although there is considerable inter-subject variability, trientine shows proportional and linear response to dosing (*Cho et al 2009*).

On the other hand, numerous studies point to the problem that treatment restrictions with regard to food intake may have a negative impact on adherence (use of medication as prescribed) and persistence (sustained use) in patients with chronic diseases, and this is also true for WD (*Masełbas et al., 2019*). For example, in the cross-sectional study by *Jacquelet et al.* (*2021*), 32.4 % of patients had low adherence according to the Morisky scale, and plasma levels of free copper were significantly higher in these patients than in those with moderate to high adherence.

From the perspective of poor adherence and the associated lack of continuity of the treatment effect, the pharmacokinetic differences between the two trientine preparations as highlighted in the present review may well be of crucial practical significance. For example, the randomized comparison of the two trientine preparations containing trientine 4HCl and trientine 2HCl, respectively, in healthy volunteers in the TRIUMPH study showed that after ingestion of equal single doses, absorption of the trientine 4HCl formulation was faster compared with trientine 2HCl (T_{max} 2 vs. 3 hours), and 68 % higher peak plasma levels (C_{max}) and a 56 % higher systemic exposure (AUC) were achieved (*Weiss et al., 2021*). These results can be readily extrapolated to patients with WD, as the steady-state pharmacokinetics of trientine is broadly comparable between healthy individuals and WD patients (*Pfeiffenberger et al, 2018*).

The higher bioavailability of the trientine 4HCl formulation means that the daily dose to be administered is 40 % lower than that of trientine 2HCl, and correspondingly fewer tablets or capsules are to be taken. The recommended dose for adults is 450–975 mg/day (3 to 6½ tablets) of trientine 4HCl versus 800–1600 mg/day (4–8 capsules) of trientine 2HCl; and for children 5 years of age and older it is 225–600 mg/day (1½–4 tablets) versus 400–1000 mg/day (2–5 capsules), respectively (*Cufence® Fachinformation, 2021; Cuprior® Fachinformation, 2020*). Another potential advantage of the trientine 4HCl preparation could be that the tablets are smaller than the hard capsules of trientine 2HCl and also divisible. This makes the medication easier to ingest, especially for very young patients, and also allows the physician to adjust the dose more precisely during lifelong therapy.

Moreover, the faster absorption and the achievement of higher plasma levels during the first 30–60 minutes after ingestion of trientine 4HCl suggest that minor adherence failures, i.e., thoughtless food intake or meals required by special individual circumstances before the end of the recommended 1-hour fasting interval after drug ingestion, will result in less loss of efficacy than would be the case with trientine 2HCl. The packaging of the trientine 4HCl preparation could also make everyday therapy easier for patients: Cuprior® is available in blister packs, while the Cufence® hard capsules are available in the somewhat more cumbersome glass bottles, which must also be kept tightly closed at all times to protect the hygroscopic dihydrochloride from moisture. In terms of therapy costs, the two preparations are largely comparable.

Conclusions for Clinical Practice

- Wilson's disease requires lifelong drug therapy, with dosage adapted to symptoms and copper levels in order to continuously eliminate the copper accumulating in the body due to the genetic defect.
- Symptomatic patients are initially treated with D-penicillamine according to guidelines. If unacceptable side effects occur (see Metalcaptase® Fachinformation), treatment is switched to a better tolerated trientine preparation. Both D-penicillamine and trientine are copper chelating agents.
- Trientine must be taken orally at least twice daily on an empty stomach – 2 hours after or at least 1 hour before a meal – because absorption is significantly impaired by food intake. This requires patients to plan their daily drug regimen in a complex manner and poses the risk of adherence problems.
- In a direct comparison of the two trientine preparations containing the trientine dihydrochloride and tetrahydrochloride salt, respectively, in fasting subjects, the TRIUMPH study found that with the tetrahydrochloride (trientine 4HCl) peak plasma levels were reached significantly faster after ingestion and bioavailability was much higher than with dihydrochloride (trientine 2HCl).
- These differences in favor of trientine 4HCl were already evident in the first hour after ingestion. This indicates that violations of the food abstinence requirement, i. e., ingestion of food before the end of the one-hour fasting period after drug ingestion, will probably lead to a smaller decrease in drug exposure in the case of treatment with trientine 4HCl, and thus a more continuous therapeutic effect will be achieved as compared to trientine 2HCl.
- It is also likely to be an advantage that fewer tablets of the trientine 4HCl formulation have to be taken and that the blister packs are a form of packaging suitable for everyday use.

Expert Comment

- WD patients and healthy subjects demonstrate similar trientine pharmacokinetics, though with considerable inter-subject variability.
- Both drug absorption and food intake affect serum concentrations of trientine.
- The formulation containing the 4HCl salt of trientine is characterized by a more favourable pharmacokinetics in terms of bioavailability and absorption compared with the 2HCl-containing formulation.
- The increased systemic exposure of trientine 4HCl translates into a reduced pill burden.

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