Current anti-copper therapies in management of Wilson disease

Isabelle Mohr[#], Karl Heinz Weiss[#]

Internal Medicine IV, University Hospital Heidelberg, Heidelberg, Germany

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Prof. Dr. Karl Heinz Weiss. Internal Medicine IV, University Hospital Heidelberg, INF 410, 69120 Heidelberg, Germany. Email: Karlheinz.weiss@med.uni-heidelberg.de.

Abstract: In Wilson disease (WD) severity of disease can vary widely, depending on time of diagnosis. Early treatment can prevent the development of symptoms in patients. In all patients, lifelong medical treatment is indicated. Currently available medical regimens include the copper chelators for example D-penicillamine (DPA) or trientine (TETA), acting to increase copper excretion and zinc salts (ZS), which reduce copper uptake. In this chapter, we discuss considerations regarding choice of drug and safety limitations.

Keywords: Trientine (TETA); anti-copper-drugs; zinc; D-penicillamine (DPA)

Introduction

Wilson Disease (WD) is an autosomal recessively inherited disorder of copper metabolism caused by mutations in the *ATP7B* gene (1,2), which codes for a transmembrane copper transporting ATPase (3,4). WD is a rare with an estimated prevalence of symptomatic disease of 1 in ~30,000 with a heterozygous *ATP7B* mutation carrier frequency of 1:90 (almost 1% of a population). Mutations in ATP7B result in impaired biliary copper excretion with consecutive copper overload primarily in the liver and later in the brain causing hepatic and neuro-psychiatric symptoms. All available therapies aim to restore a negative copper balance. Their use—or the choice of the treatment—is driven by different safety and efficacy consideration as well as by the clinical presentation of the patient and previous exposure to anti-copper drugs. Current guidelines (5,6) discriminate treatment regimens as initial (decoppering) or long-term (maintenance) therapies. After the initial, more potent treatment phase aiming for a negative copper balance, a reduced dose of the chelating agents might be sufficient for maintenance of copper homeostasis.

D-penicillamine (DPA) was introduced as the first oral copper chelator by Walshe in 1956 (7) and saved thousands of WD patients worldwide. Alternative anti-copper drugs with in improved safety profile followed with zinc salts (ZS) in the 1960s (8) and with trientine (TETA) in the 1980s (9).

Medical needs

Concerning patient compliance, certain phenotypes can be described, divided in three with a divergent mortality and morbidity: "the incompliant patient, the patient with fulminant hepatic failure and the symptomatic neurologic patient" (10).

Once the diagnosis is made, lifelong treatment and monitoring of adherence is necessary. Non-compliance and as a consequence uncontrolled copper balance are main risk factors for hepatic failure or neurological deterioration (11). In the light of studies suggesting a high rate of patients with problematic long-term adherence (12), measures to prevent incompliance and to improve adherence are essential. Thus, the ideal treatment regime scheme should be as simple as possible (10) and efficacy of the current anti-copper regimen should be re-evaluated in any case of disease progression (5,6).

Overall, the efficacy of chelating agents and/or zinc is

satisfactory for hepatic disease manifestations, except in patients developing acute liver failure (formerly referred to as "fulminant Wilson disease") in whom still liver transplantation might be the only lifesaving therapy. Validated scores can guide the decision whether an urgent liver transplantation is needed or not (13,14).

Still disappointing results—in regard to treatment response—are seen in a large proportion of patients with neurological symptoms. The optimal treatment of neurologic disease is—in these authors opinion—the most pressing medical need in WD. For sure, the disappointing neurologic response can in part be explained by the irreversibility of structural neurologic damage. But still, paradoxical neurological deterioration after the initiation of chelation therapy is an unexplained unfavorable course.

Choice of drug for initial treatment

In WD only few randomized controlled trials and thus the available medical treatment options are still not standardized. Treatment recommendations are largely based on clinical experience and cohort studies and driven by safety concerns. The clinical presentation of the patient might drive treatment decisions according to the following rationales:

  ❖ In asymptomatic patients or patients with only mild hepatic symptoms all available agents have the desired effect (11,15-21). The choice of the drug—chelators versus ZS—should primarily be driven by safety considerations (10). Concerning chelating agents this favors TETA over DPA (22,23).
  ❖ In patients with hepatic manifestation, the degree of liver damage determines the further clinical course. From a hepatologist's perspective a liver cirrhosis is a liver cirrhosis—and comes with all the implications regarding monitoring and treatment of portal hypertension that in any other liver patient with a different etiology. In WD, chelators establish a negative copper balance faster than ZS (21,24,25). We have previously reported a hepatic improvement with DPA or TETA in more than 90% of symptomatic hepatic cases (23).
  ❖ In case of symptomatic neurologic patients, therapy is less successful with at least a third of patients not profiting by medication (23). Clinical response rates to chelation therapy are in same ranges as reported for zinc monotherapy with regard to symptomatic neurologic patients (16,26). This fact

could be explained by the concept of an irreversible cell damage in the central nervous system, which is already established at time of diagnosis (10,27).

Most troublesome however is the reported paradoxical worsening of the neurological symptomology in up to 20% of WD patients after initiation therapy (16,28-30). In up to half of the patients showing such deterioration, the neurologic disease progression might be even irreversible (31). Several reports suggest that this worsening might be associated with chelating agents [especially DPA (30)], but it seems to occur under zinc as well (31).

An approach to address safety issues—especially with regard to prevention of neurologic deterioration—might be a careful and systematic monitoring of biochemical markers [e.g., non-ceruloplasmin-bound copper (NCC), urinary copper, etc.] as well as a continuous monitoring of clinical symptoms using validated rating scales such as the unified WD rating scale (UWDRS) (10).

Available drugs for WD are listed in *Table 1* [modified from (5) and (6)], that we will discuss drug by drug in the following paragraphs.

DPA

The major effect of DPA is to stimulate and extend the urinary excretion of copper. The recommended maintenance dose is 750–1,500 mg/day (20 mg/kg/day rounded off to the nearest available dose), administered in two or three divided doses (5).

DPA should be taken about one hour prior to meals, because gastrointestinal absorption is inhibited food. In case it is administered together with a meal, absorption can be decreased by about fifty percent (5). In addition, DPA interferes with pyridoxine metabolism why excess pyridoxine should be supplemented (25–50 mg/day).

Twenty-four-hour urinary copper excretion is recommended for treatment monitoring. Collection procedures vary among centers with some—especially European centers—supporting urinary copper excretion measurements after 2 days off chelating agents. However, especially in the initial treatment phase, urinary copper measurements on drug (without any interruption) might be more informative. Urinary copper per day is usually highest during initiation of treatment and should be three to eight μmol per twenty-four hours (equivalent to 200–500 μmol/24 h) (5). In long-term monitoring, the most important sign of efficacy are clinical and laboratory improvements. It is observed

Table 1 Drugs used in the treatment of WD [modified from EASL (5) and AASLD (6) practice guidelines]

Drug	Mechanism	AE under drug therapy that should be monitored	Efficacy monitoring by 24 h urine copper and NCC
DPA	Chelating agent/facilitates urinary excretion of copper	20–30% during treatment: (I) hypersensitivity; (II) arthralgia; (III) leukopenia; (IV) proteinuria; (V) paradoxical neurological worsening; (VI) renal impairment; (VII) gastric symptoms	(I) at the beginning of the treatment copper urinary excretion >1,000 µg/24 h; (II) under therapy with DPA, copper urinary excretion about 200–500 µg/24 h; (III) serum NCC 5–15 µg/dL
TETA	Chelating agent/facilitates urinary excretion of copper	5–10% (less than with DPA): (I) sideroblastic anemia (commonly indicative of overtreatment); (II) paradoxical neurological worsening	(I) at the beginning of the treatment copper urinary excretion >1,000 µg/24 h); (II) under therapy with DPA, copper urinary excretion about 200–500 µg/24 h; (III) serum NCC* 5–15 µg/dL
ZS	Inhibits intestinal absorption of copper	3–7%: (I) gastritis; (II) biochemical pancreatitis	(I) copper urinary excretion <75 µg/24 h; (II) serum NCC 5–15 µg/dL (>12 months of treatment)

NCC is not routinely used. *, NCC <5 µg/dL indicates over treatment and modification of therapy might be needed. Decrease of NCC during treatment is currently used as an efficacy measure. WD, Wilson disease; NCC, non-ceruloplasmin-bound copper; DPA, D-penicillamine; TETA, trientine; ZS, zinc salts.

that serum ceruloplasmin may decrease after initiation of decoppering therapy.

Therapeutic efficiency is reached when urinary copper excretion reached a steady state, usually between 2–5 times upper limit of normal (UNL). This might correspond to measures less than 1.6 µmol per day after two days of chelator intermission. Additionally, NCC reveals normalization under effective treatment (32). Serum NCC under treatment should be 5–15 µg/dL (5,12,33).

DPA is rapidly absorbed from the gastrointestinal mucosa. The greatest amount of DPA is bound to plasma proteins such as albumin (about 80%). The free percentage of DPA becomes inactive by forming dimers or binds to other plasma proteins e.g., cysteine (6). Total bioavailability is estimated at 40–70%, depending also on correct administration (6). Major amount of DPA is discharged via the kidneys. The excretion half-life (t ½) of DPA is variating because of individual metabolism as well as of medication administration (t ½ =1.7–7 hours) (5,6).

The effectiveness of DPA as well tolerated treatment for WD has been proven in numerous clinical studies (16,30,34). In patients with symptomatic liver disease, recovery of liver function (quick, albumin, cholinesterase) and improvement in clinical signs (e.g., less fatigue) typically occurs during the first six to twelve months (5).

Nonadherence to therapy leads often to significant progression, inducing acute liver failure within few months. In symptomatic neurological patients, improvement of symptoms is observed to be slower and may be even awaited after some years (1–3 years) (5,35). Neurological deterioration is reported especially during initial phase of treatment in 10–30% of patients under DPA therapy (30).

When starting with gradual doses (between 150–300 mg/day) which can be increased slowly every week till the maximum dose is reached, tolerance can be exaggerated and undesirable side effects limited (5). Very fast dose escalations as well as re-administration after a longer therapy pause seem to be associated with potentially irreversible neurological deterioration (30,31).

DPA is associated with numerous side effects, which in approximately 30% of patients require discontinuation (34,36). These can be divided in early adverse events (AE) within the first three weeks and late AE's, which might come up after years.

Early sensitivity reactions are marked by drug fever and cutaneous manifestations including generalized pruritus and rashes, lymphadenopathy or depression of blood cells (neutropenia, thrombocytopenia or total aplasia in case of bone marrow depression) (6). Even proteinuria might be detected by urinary status during the first weeks and is also recommended to be checked regularly under treatment as a monitoring instrument (5). Severe thrombocytopenia or total aplasia as well as newly diagnosed proteinuria require immediate discontinuation of DPA treatment (10). Mostly, this can be observed in cases of over dosing.

Late onset side effects include progressive proteinuria or the seldom Goodpasture syndrome with fatal glomerulonephritis and intra-alveolar haemorrhage. These findings of nephrotoxicity should lead to discontinuation of DPA (16). Other long-term reactions span from mild symptoms, such as gastric symptoms, hair loss or hypogeusia to myasthenia- or lupus-like syndrome marked by hematuria, positive antinuclear antibody (4,6).

Dermatological toxicities are reported more frequently,

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including structural changes in the skin. Elastosis perforans serpiginosa, pemphigus or pemphigoid like lesions, lichen planus or aphthous stomatitis are the most frequent ones to name (6,37).

DPA should not be combined with agents of the following classes because of pharmacological interactions: myelosuppressive or cytostatic agents, antimalarials, oxyphenbutazone and phenylbutazone (4). It interacts also with other (heavy) metals, why administration should be timely separated from zinc and iron uptake.

TETA

In 1969, TETA was introduced as an alternative to DPA. TETA is also a chelator but its chemically structure is distinct from DPA lacking sulfhydryl groups. Like DPA, TETA increases urinary copper excretion.

In contrast to DPA, TETA gastrointestinal absorption is less efficient (5). The absorbed drug is metabolized and inactivated in relevant amounts (6): directly, about one percent of the administered TETA and about eight percent of the biotransformed metabolite (acetyltrien) are excreted via urine (6).

In comparison with TETA, its metabolite (acetyltrien) binds copper less effective (6). The mobilized copper is like DPA discharged via the kidneys. The discussion of whether TETA is a weaker chelator of copper than DPA is still controversial in recent studies (6,16,38). Nevertheless, both agents seem to target different pools copper (6,38).

TETA is accepted as an alternative drug to DPA with potential, especially in patients that suffer from side effects of DPA or have clinical features indicating prospective intolerance (6,9,29). In contrast to DPA, neurological worsening under TETA initiation phase has been detected less common (6). Moreover, a hepatic improvement with TETA is reported in some studies in more than ninety percent of patients with hepatic symptoms (23).

Treatment monitoring is analog to DPA by measuring twenty-four hours urinary copper excretion without treatment pause (see reference values above). The NCC may show normalization under effective treatment. NCC is a good parameter of dosing and adherence. In patients with nonadherence to therapy, NCC is usually enhanced (reference values: 15 to 150 µg/dL) (6). If NCC values are very low (5 to 50 µg/L), this might indicate overdosing (6).

Recommended dosages of TETA are between 900–2,700 mg/day during treatment initiation and between 900–1,500 mg/day (20 mg/kg/day) used for maintenance (5,6). Like DPA, doses should be divided into several portions. Guidelines recommend to take TETA one hour before or several hours after meals. TETA needs to be cooled if the tablet is exposed to high temperatures, because the active agent is not heat-resistant (6).

TETA has a few side effects, AE are four-fold less than in DPA. Severe hypersensitivity reactions have not been reported yet, except a fixed cutaneous drug reaction which was observed in one patient (6). A reversible sideroblastic anemia may be a consequence of overtreatment and resultant copper deficiency. Pancytopenia has been observed in some cases. Lupus-like syndrome has also been reported in some patients as well as hemorrhagic gastritis, loss of taste and rashes (6,39).

Zinc

The pharmacological mechanism of zinc is different from DPA and TETA: zinc competes with the uptake of copper in the gastrointestinal mucosa. Zinc induces metallothionein—a cysteine-rich protein—in the enterocyte, which functions as an endogenous chelator of metals.

Metallothionein binds copper with greater affinity than zinc and thus, preferentially binds copper. This indirectly stops copper uptake to the blood circulation (26). The copper is somehow trapped in the enterocyte and excreted into the fecal contents by normal cell turnover (26). Zinc treatment can generate a negative balance for copper (40,41). Zinc may also induce elevated levels of hepatocellular metallothionein, enhancing cellular copper storage capacity (42,43). Different zinc salts for example sulphate, acetate or gluconate are available, but pharmacodynamics data favors zinc acetate (5). The recommended dose is a maximum of 150 mg elemental zinc per day divided in two to three dosages before food uptake, because its food interferes significantly with its with its absorption (5,6,44).

In combination therapy with chelators different times of dosing have to be considered to avoid interaction (see paragraph TETA above).

Monitoring of treatment with zinc is follows clinical and biochemical improvement. Like monitoring of DPA or TETA, twenty-four hours urinary excretion of copper can be used. Values should be less than 1.6 µmol per day on stable treatment (<75 µg/24 h) (5,6). Additionally, NCC should drop with effective treatment >12 months (NCC 5–15 µg/dL). Urinary zinc amount can be occasionally quantified to check patient's adherence (5).

Zinc has some side effects. Gastric irritation is

common in about 30% of patients (5). Zinc may have immunosuppressant effects by reducing leukocytes and causing a bone marrow depression (8,40). Increased serum lipase/amylase might be measured, without any—clinical or radiologic—sign of pancreatitis (5,41). Neurological deterioration is not reported under zinc monotherapy (6,16,45).

Nevertheless, zinc as monotherapy during initial decoppering phase might be not as effective as a therapy with chelating agents (22), but seems to be equal for therapy maintenance. Moreover, it is recommended as first-line therapy for asymptomatic patients, better tolerated as e.g., DPA (5,6,41). While zinc monotherapy is safe in neurological and in asymptomatic patients, hepatic deterioration is reported in some cases of patients with hepatic manifestation (5,45). In a subpopulation of patients, zinc monotherapy is insufficient to control hepatic disease (46,47).

In summary, exclusive monotherapy with zinc in symptomatic Wilson liver disease requires monitoring for efficacy as well as for possible side effects.

Treatment sequences and maintenance therapy: consequences for long term monitoring

The overall goal of treatment monitoring is to ensure clinical and biochemical improvement, assess compliance and screen for AE necessitating modifications of the medical regime.

This includes the assessment of when the patients leave the decoppering phase and enter into maintenance therapy. In clinical practice this time point if surprisingly unclear, as there are no commonly accepted definitions of when a patient is "de-coppered".

From a biochemical point of view for a copper overload disorder, a response guide therapy seems a logical consequence, taking into account the treatment related changes of measurable copper parameters (48,49). An analysis daily urinary copper excretion (under ongoing medication) reflects overall exchangeable copper and is helpful for monitoring as well as for compliance. Target ranges of 24-hour urinary copper excretion under DPA, TETA and zinc are already mentioned above. If values for urine copper are elevated, this might be indicative of poor adherence or underdosing. Low values for urine copper excretion under chelation treatment could also indicate overtreatment while NCC values are typically low (33).

Non-ceruloplasmin-bound copper (or "free copper") can be calculated by subtracting ceruloplasmin-bound copper from the total serum copper concentration: NCC = [total serum copper (µmol/L) –0.049] × ceruloplasmin (mg/L) (5). The amount of copper associated with ceruloplasmin is approximately 3.15 µg of copper per milligram of ceruloplasmin. The usefulness of this calculation in WD has been subject of intensive discussions in the field. The value of ceruloplasmin levels determined by immunological methods has been questioned due to the high values measuring falsely high Cp values, as these tests do not discriminate between holo-ceruloplasmin and apo-ceruloplasmin (50,51). When using immunological tests, negative NCC values for NCC might be found up to 10 to 25% of WD patients (52-54). NCC is elevated above 25 µg/dL (250 µg/L) in most untreated patients (normal 15 µg/dL =150 µg/L) and should decline under anti-copper-therapy. NCC concentrations <5 µg/dL (<50 µg/L) could be a signal of systemic copper depletion which is possible in patients a prolonged treatment.

Long-term intake of subtherapeutic dosages may also present with low values for 24-hour urine copper excretion, while having elevated NCC values. Urine analysis as well as total blood count should be performed regularly to assure safety under chelation therapy to detect adverse proteinuria or anemia (33).

Conclusions

Improved diagnostic techniques and more systematic approaches in diagnosis offer an easier path to confirmation or exclusion of a diagnosis of WD and therefore an earlier treatment. Currently used ZS and chelators are mostly effective but have some limitations, chelating agents being associated with a deterioration of neurological symptoms. Future clinical trials should aim for better defining dosing, ideally offering comparative effectiveness of available medical therapies and standardization of definitions for treatment success and failure. The concept of different copper pools renders "control of free circulating copper" a primary monitoring readout. However, broad clinical evidence is lacking to allow general recommendation for dosage adjustments based on the Serum copper status alone. Currently NCC, urinary copper excretion as well as for other biochemical markers can only be seen as broad guidance, but not as read out parameters of a response guided therapy. All biochemical parameters (liver function) and clinical features (course of neurologic symptoms) should be taken into account regarding dosage decisions.

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Acknowledgements

Footnote

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