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EXPERT OPINION

Treatment of Wilson's disease – another point of view

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1. Introduction

We would like to present a different opinion to that of Dr. Brewer [1]. There is no doubt that Dr. Brewer has a great experience and has worked for a long time with Wilson's disease (WD) patients; however, his point of view is incompatible with recent recommendations prepared by international bodies, the American Association for the Study of Liver Diseases (AASLD) [2] and the European Association for the Study of Liver Diseases (EASL) [3]. This may cause a lot of confusion for less experienced physicians and prevent many patients from accessing currently available treatment.

Currently, according to international recommendations and drug regulatory agencies WD should, in the great majority of cases, be treated pharmacologically. Liver transplantation is recommended only for patients with fulminant liver failure and for those with progressing liver failure despite pharmacological anticopper treatment [2,3]. There is no data proving that liver transplant may reverse neurological deficit; however, some anecdotal cases are available in the literature [2,3].

The pharmacological treatment of WD consists of drugs leading to a negative copper balance such as: i) chelators (D-penicillamine [DPA] or trientine), which induce urinary excretion of copper; and ii) zinc salts, which mainly decrease copper absorption from the digestive tract (by induction of metallothionein synthesis).

Tetrathiomolybdate has a dual mechanism of action; forming complexes with copper to prevent copper absorption from the gut as well as forming complexes with copper in the blood making this metal unavailable for cellular uptake. Despite the fact that preliminary studies with tetrathiomolybdate are promising at present [1], it cannot be recommended for either initial or drug-resistant patients. Further studies are needed.

It is important to note, when considering pharmacological treatment, that there are no prospective, randomized studies directly comparing the safety and efficacy of drugs used in WD treatment. At present, only reports with conflicting data about the superiority of different drugs used in WD treatment that are based on retrospective studies from different countries, performed by different specialists (hepatologists, neurologists, pediatricians) are available. This leads to slightly different treatment strategies in different countries and at different centers. However, the above-mentioned recommendations (AASLD and EASL) [2,3] advise that initial treatment for symptomatic WD patients should be chelators (DPA or trientine; there is just suggestion that trientine is better tolerated) [3]. These guidelines also recommend that zinc salts could be used as a first line of treatment in patients with neurological symptoms and in those who are presymptomatic. In addition, zinc salts could also be used as a maintenance therapy for WD patients.

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In our present paper, we will discuss whether Dr. Brewer is correct in suggesting that DPA should not be used in neurological patients. We also postulate that DPA and zinc salts are equally effective for treating WD, irrespective of the clinical form.

Similarly to Dr. Brewer, we have a great deal of experience with managing WD patients, with > 750 cases diagnosed in our center since 1960s. These patients begun therapy here and most have been on long-term follow-up with us.

2. Treating with DPA or zinc

Our experience is limited to DPA and zinc sulfate (ZS). DPA has been available in Poland since the 1960s, and we began to use ZS in the mid-1980s. Both drugs are easily available to patients. Trientine or other zinc formulas, on the other hand, are much more expensive and not reimbursed in Poland.

It is not to be discussed that the discovery of DPA by John Walshe in 1956 has dramatically changed the prognosis of WD all over the world. DPA ameliorates clinical symptoms, saves lives and can protect patients from developing the clinical presentation of the disease [2,3]. However, there are no drugs without side effects, nor any which all patients respond satisfactorily to. This is the reason that we started to use ZS after reading Hoogenraad paper from 1979 [4] and others (who confirmed studies from 1961 done by Schouwink, unfortunately publish only as PhD thesis in Dutch). Fortunately, ZS was easily accessible in our country.

Since that time, we have published papers discussing the results of treatment with both drugs [5-9]. All of our observations show that in general, both types of therapy can be introduced to newly diagnosed patients and that there are no substantial differences in clinical improvement, early neurological deterioration or mortality. We did find that adverse reactions were more common in the DPA group [5-9].

Our papers published in the years 1996 – 2014 differ in methodology. Unfortunately, they weren't randomized, and selection to type of treatment mostly depended on physician discretion and sometimes on the availability of drugs on the market. In our most recent study, we followed 143 consecutive patients who were newly diagnosed with symptomatic WD, 56 with the neurological form and 87 hepatic. Seventy-one patients received DPA and 72 received ZS as initial treatment [6]. In contrast to the above-mentioned recommendations [2,3], DPA was given more frequently in neurological patients (62%) than in hepatic patients (41%). The median observation was 4 years (IQR3-5). Most of the patients remained on the same drug (DPA 80%, ZS 76.2%). In 87% of the neurological patients, clinical improvement was observed on DPA while improvement was observed in 80% on ZS. Eighteen (25%) patients on DPA changed to ZS, but only 11 (15%) changed from ZS to DPA. In the hepatic patients, complete or partial enzymatic improvement was observed on both drugs with a similar frequency (97 and 94%), 11 (30%) on DPA changed to ZS, but only 6 (12%) changed from ZS to DPA. It has to be noted that in both groups the patients who started on DPA therapy were slightly more severely ill than patients on ZS. This was due to our long-term positive experience with DPA and our consideration that it is a faster (stronger) acting drug [6].

We also followed 87 presymptomatic WD patients for a period of 3 – 52 years (median 12). Thirty-two percent of them were treated with DPA (until the 1980s only DPA treatment was possible), and 67% with ZS. Development of hepatic (15%) or neurological (24%) symptoms were not dependent on the type of therapy, according to a multivariate analysis of DPA versus ZS (OR 1.50; 95% CI 0.30–7.44), but the result was mainly owing to poor compliance [7].

3. Neurological deterioration

Dr. Brewer and other authors emphasize that the greatest cause of contraindication to use of DPA as an initial therapy is early neurological deterioration, often not reversible, which may occur in 50% of cases [10,11].

The mechanism of early neurological worsening in WD patients is still unknown. Some observations of copper metabolism in the serum and CSF of newly diagnosed WD patients showed a rapid increase of copper with increased oxidative stress during the initiation of chelator therapy [12,13]. Currently, chelators are very slowly introduced in WD, decreasing the ratio of neurological worsening to 10% [14]. The latest study performed by Weiss *et al.* [14], surprisingly showed a similar ratio of neurological worsening on all schemes of WD treatment (ZS – 9.5%, DPA – 9.1% and trientine – 8.8%), thus partially disrupting the hypothesis that chelators acting too quickly predict neurological worsening. We have also addressed this problem in our studies. In a 1996 paper, we didn't notice a higher rate of deterioration between the ZS and DPA groups [5]. Similarly, in the recent paper mentioned above [6], early neurological worsening (up to 6 months after treatment initiation) was observed in 11% of 143 patients but only in those with the neurological form of the disease. The neurological deterioration was completely reversible in 53% (8/15) patients and partially reversible in 13% (2/15) patients during 9.2 ± 5.2 months. Baseline neurological symptoms, advance of neurological deficits, changes in thalamus and brain stem appearance on MRI and concomitant treatment with drugs potentially modulating the action of dopamine were the main predictors of early neurological deterioration. The type of WD treatment (DPA or ZS) had no impact on the possibility of early neurological worsening (our unpublished data). Greater risk of deterioration of patients with more severe neurological signs and greater changes in MRI may indicate that initial brain injury is a major risk of deterioration, independently of type of therapy. The course of both hepatic and neurological symptoms is always difficult to predict when therapy is initiated. Despite treatment, brain damage may progress because the drugs are acting too slowly or because when therapy was begun there

Table 1. The possible drug-related adverse reactions during Wilson's disease (WD) treatment.

The WD drug	Possible adverse events
D-penicillamine	A) Acute drug reactions (occurring during the first 3 weeks of treatment) — Proteinuria, leucopenia and thrombocytopenia — Lymphadenopathy — Allergic reactions (with fever, erosions, skin changes) B) Late drug reactions (occurring after 3 weeks of treatment) — Nephritic syndrome (Goodpasture syndrome) — Skin reaction (progeric changes, elastosis perforans serpiginosa) — Lupus like reaction (hematuria, proteinuria, presence of serum antinuclear antibodies); — Serous retinitis — Hepatotoxicity; — Leukopenia, thrombocytopenia; — Loss of taste — Myasthenia gravis - like syndromes
Trientine	Gastritis Sideroblastic anemia Lupus-like reactions Loss of taste
Zinc salts	Gastritis Biochemical pancreatitis Immunosuppression Bone marrow depression

was already permanent brain damage. Similarly, as we cannot reverse acute hepatic failure, sometimes we cannot reverse brain damage. It is also worth stressing that concomitant medication as metoclopramide or antipsychotic drugs may further impair brain functions.

4. Adverse drug reactions

During DPA treatment, according to a recent study performed in 2013 by Weiss *et al.*, almost 30% of patients reported adverse reactions leading to treatment discontinuation (the most important cause of treatment failure) [14,15]. Apart from early neurological deterioration, the adverse reactions due to DPA therapy could be divided into: i) acute drug reactions; or ii) late drug reactions (**Table 1**). However, despite the list of various adverse reactions, in our last study of 72 patients who started treatment with DPA we found that only 11 (15%) of cases of adverse reactions led to a change in treatment (leucopenia 1, albuminuria/proteinuria 5, abdominal pain 2, skin rash 2, thrombocytopenia 1) [6]. We must remember that even before therapy, many WD patients have low white blood cell and platelet counts. Late adverse reactions are also not common. In our registry, we have only three cases of Goodpasture syndrome, two lupus-like syndrome, two myasthenia, two elastosis perforans serpiginosa. Progeric changes in skin are common after long-term therapy, particularly in females, but this is rarely severe. ZS seems to cause fewer severe adverse reactions, most frequently gastritis (stomach pain) or an increased level of pancreatic enzymes (without clinical signs) [2,3]. Of 72 patients who started treatment with ZS we found that only 2 (2.7%) of cases of adverse reactions caused a change in treatment (skin changes, thrombocytopenia) [6]. We noticed that patients who experience stomach pain when taking either therapy should take the medication half an hour after their meal, but not on empty stomach. There are no studies comparing adverse reactions depending on zinc salt formulations.

We also have to be aware that long-term anticopper treatment may lead to copper deficiency.

Anticopper therapy led to a decrease in non-ceruloplasmin-bound copper in blood (free copper), which in WD patients is higher and responsible for copper accumulation in tissues. Normal values are between 5 and 15 μg/dl. However, overly excessive anticopper treatment may cause a fall of copper concentration below 5 μg/dl [2,3], which may lead to copper deficiency syndrome [2,3,16].

Hypocupremia manifests as myeloneuropathy and blood dyscrasia resembling vitamin B12 deficiency [16]. The typical neurological signs are spastic gait and sensory ataxia with increased signal of dorsal column in cervical and/or thoracic cord on T2-weighted MRI images and impaired dorsal column somatosensory-evoked potentials. Less commonly reported symptoms are isolated peripheral axonal neuropathy. The hematologic manifestations include sideroblastic anemia, neutropenia and occasionally thrombocytopenia [16].

Careful hematological monitoring and neurological investigations can help to identify copper deficiency. Clinical signs of myelopathy or peripheral nervous symptoms are in fact not observed in WD, so their appearance requires immediate attention.

It has to be emphasized that regular monitoring of basic laboratory tests and copper metabolism is advised in all recommendations. However, the method of measuring free copper in the blood is not standardized. Most commonly free copper is calculated from the level of ceruloplasmin and whole copper in blood. At present, different labs use various methods of measuring ceruloplasmin [2,3].

5. Compliance

Finally, we would like to discuss the problem of compliance. Despite having good drugs, many of our patients deteriorate or even die due to treatment resignation or non-adherence to a prescribed scheme of therapy [7,8,17]. Similarly, as in other chronic diseases, it is difficult for patients to be compliant with treatment for all of their life. Most papers addressing this problem report that 20 – 45% of WD patients are uncompliant, without remarkable differences between drugs [2,3,7,8]. Apart single-drug questionnaires for WD patients, which help to control the correct anticopper drug intake,

analysis of copper metabolism (and zinc in cases of ZS therapy) must be performed on at least a biannual basis to verify the adequacy of treatment. For all of the anticopper drugs, the unbound copper level should be between 5 and 15 µg/dl; however, as mentioned above the method of measurement isn't standardized. Measuring levels of copper urinary excretion may also be helpful to ensure compliance. In cases properly treated with ZS, 24-h copper excretion should be below normal values. In cases treated with chelators, copper levels should be between 300 and 500 µg/24 h, however, great variation is seen. In European recommendations, it is mentioned that patients correctly treated with DPA for over 1 year should have urinary copper levels the same as a healthy control from 2 days following cessation of treatment [3]. However, this method is also not standardized.

We did not discuss treatment with trientine, but based upon current literature efficacy is similar to DPA. Due to its later introduction, registration problems and cost, it is less commonly used [2,3].

6. Conclusions

In summary, WD is a genetic disorder that can be successfully treated with pharmacological agents: chelators or zinc salts depending on center experience [5,6,18,19]. DPA cannot be excluded from drugs recommended for WD patients. Compliance and treatment monitoring seem to be more important in WD treatment than the choice of drug.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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