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[Intervention Protocol]

Medical therapeutic agents for Wilson's disease

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the beneficial and harmful effects of copper-chelating agents in treating patients with Wilson's disease.

BACKGROUND

Description of the condition

Wilson's disease is an autosomal recessive disorder of copper metabolism with a worldwide distribution. The average prevalence of the disease is 30 individuals per million population (Frydman 1990), whereas even higher numbers are observed in areas of consanguinity (Rahil 2010). Wilson's disease is caused by mutations in the ATP7B gene localised on chromosome 13q14.3,6 encoding the ATP7B protein. This protein is responsible for transport of copper across cellular membranes using ATP as an energy source (Cater 2006).

Presentations of Wilson's disease are variable depending on the affected organs. The main two presentations are liver and neuropsychiatric manifestations. Patients either present acutely with liver failure, haemolytic anaemia, or both, or more chronically with liver conditions such as chronic hepatitis, portal hypertension, or cirrhosis (Schoen 1990). In other patients, it may present with neuropsychiatric manifestations, including movement or dystonic disorders, dysarthriae, and behavioural disturbances (Merle 2007). Kayser-Fleischer ring - a pigmented ring at the outer edge of the cornea of the eye - is a characteristic sign of Wilson's disease (Gitlin JD 2003; Ala 2007).

The diagnosis of Wilson's disease is proved by measurement of serum ceruloplasmin, urinary copper excretion, and hepatic copper content, as well as the detection of Kayser-Fleischer rings (El-Youssef 2003). Early diagnosis of Wilson's disease is essential, as treatment of the disease is more effective when initiated early (Medici 2007). Wilson's disease becomes fatal if left untreated (Sternlieb 2005) with a mortality as high as 70% (Chang 2010). Patients with fulminant liver disease can be treated with liver transplantation (Markiewicz-Kijewska 2008).

Description of the intervention

Current treatment of Wilson's disease includes copper-chelators, such as D-penicillamine, trientine, and tetrathiomolybdate, as well

as zinc salts. Lifetime therapy is required in patients with Wilson's disease. Once the diagnosis is secure, whether or not the patient is ill or asymptomatic, treatment should be given in two phases. The first is removing the tissue copper that has accumulated, and the second is preventing re-accumulation of copper (Wiggelinkhuizen 2009). D-penicillamine is the primary chelator (Roberts 2003). However, approximately 30% of patients do not tolerate long-term therapy because of adverse events, and it may not be the treatment of choice in patients with neurologic symptoms. Zinc seems to be preferred above D-penicillamine for treatment of presymptomatic and neurological patients. Trientine has traditionally been used as a second-line agent, but it is also a reasonable option for primary therapy, and it may be the preferred treatment because of lower association with adverse events (Wiggelinkhuizen 2009). The best therapeutic approach for each specific presentation of the disease remains controversial, and there is no universally accepted regimen (Ala 2007).

How the intervention might work

Penicillamine and trientine bind to copper in the body, resulting in its increased urinary excretion, whereas tetrathiomolybdate acts by forming a tripartite complex with copper and protein, either in the intestinal lumen where it prevents copper absorption, or in the circulation where it makes the copper unavailable for cellular uptake (Walshe 1956; Jones 1984). Zinc acts by blocking the carrier in the intestinal epithelial cells for copper transport (Yuzbasiya 1992; Jablonska-Kaszewska 2003). In addition, it increases the levels of metallothionein in enterocytes that acts as an intracellular ligand binding copper and holding it until it is excreted in the faeces with desquamated epithelial cells (Yuzbasiya 1992; Jablonska-Kaszewska 2003). Furthermore, both chelators and zinc can induce copper binding metallothionein in hepatocytes, thereby reducing the damaging effects of free copper (Goering 1985; Lee 1989).

Why it is important to do this review

Currently, the main standard treatment used for treating patients with Wilson's disease are copper-chelating agents (penicillamine, trientine, ammonium tetrathiomolybdate, and zinc salts). However, some of these drugs have severe adverse events, and unfortunately, a large proportion of patients cannot tolerate them.
During our search, we could not find meta-analyses of systematic reviews of randomised clinical trials evaluating the beneficial and harmful effects of copper-chelating agents for Wilson's disease. Thus, we found it important to study the effects of these drugs.

OBJECTIVES

To evaluate the beneficial and harmful effects of copper-chelating agents in treating patients with Wilson's disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised clinical trials assessing the beneficial and harmful effects of chelating agents for Wilson's disease, irrespective of publication status, or language. Quasi-randomised and observational studies will be excluded for the study of their benefit, but will be considered only for the report of harm.

Types of participants

We will include:
- Patients of either sex, having Wilson's disease as defined by the trialists.
- All spectrum of Wilson's disease patients, whether they are asymptomatic, or they have hepatic, or neuropsychiatric manifestations.
- Patients who are treatment-naive or treated for the first time, as defined by the trialists.

We will exclude patients who are on maintenance therapy.

Types of interventions

- Copper-chelating interventions (D-penicillamine, trientine, ammonium tetrathiomolybdate) or zinc salts versus any other kind of copper-chelating therapy or zinc salts.

Drug treatment of Wilson's disease is instituted once the diagnosis is secure whether the patient is ill or asymptomatic. Co-interventions will be allowed if administered equally to all groups of a trial.

Types of outcome measures

Outcomes of clinical improvements will be considered only if reported two to six months after the initiation of drug therapy.

Primary outcomes

1. All-cause mortality.
2. Morbidity, related to the liver (acute liver failure, chronic hepatitis and signs of hepatic decompensation such as ascites, bleeding varices, and/or splenomegaly, cirrhosis, and liver transplantation).
3. Adverse events defined as any untoward medical occurrence not necessarily having a causal relationship with the treatment,

but resulting in a dose reduction or discontinuation of treatment (ICH-GCP 1997). Severe adverse events are defined as any event that would increase mortality; is life-threatening; requires inpatient hospitalisation; results in a persistent or significant disability; or any important medical event, which may jeopardise the patient or require intervention to prevent it.
4. Quality of life.

Secondary outcomes

1. Clinical findings including:
- neuropsychiatric symptoms: number of patiens without improvement of neuropsychiatric symptoms or neuropsychiatric score.
- liver-related symptoms: number of patiens without improvement of liver-related symptom.

2. Number of patiens with drug withdrawal/drug discontinuation.
3. Number of patiens without biochemical responses (serum non-ceruloplasmin-bound copper concentration and 24-hour urinary copper excretion, and serum activities of aspartate transaminase and alanine aminotransferase).

Search methods for identification of studies

Electronic searches

We will search *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2010), *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library*, *MEDLINE*, *EMBASE,* and *Science Citation Index Expanded* (Royle 2003). We have presented the preliminary search strategies in Appendix 1 with the time span for the searches. The search strategies may need to be improved during our work on the review.

Searching other resources

The bibliographic references of identified randomised clinical trials, review articles, and meta-analyses will be checked in order to identify additional randomised clinical trials not found by the electronic searches.

Data collection and analysis

We will perform the review and meta-analyses following the recommendations of The Cochrane Collaboration (Higgins 2009) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2010). The analyses will be performed using Review Manager 5 (RevMan 2008).

Selection of studies

Two authors will independently identify trials for inclusion. Firstly, titles and abstracts of the records retrieved by the search will be assessed in order to exclude those that are irrelevant. For the remaining records, full-text articles will be retrieved and assessed in order to select trials that meet the inclusion criteria. We will list the trials excluded from the second round and give the reasons for their exclusion.

Data extraction and management

We will develop a standardised template form for data collection and extraction. Data on methods, participants, interventions and outcomes, as listed above, will be extracted.
If more than one publication on a randomised clinical trial is identified, the most recent data will be extracted.
Two authors will extract all data independently. Disagreements will be resolved by discussion among the authors.

Assessment of risk of bias in included studies

Methodological quality is defined as the confidence that the design and report will restrict bias in the intervention comparison of beneficial effects (Moher 1998). According to empirical evidence (Schulz 1995; Moher 1998; Jüni 2001; Kjaergard 2001; Wood 2008), evaluation of the risk of bias could be achieved through assessing the following domains:

Sequence allocation generation

- Low risk of bias. Sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent adjudicator.
- Uncertain risk of bias. The trial is described as randomised, but the method of sequence generation was not specified.
- High risk of bias. The sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are studies with high risk of bias and will, therefore, be excluded for the assessment of benefits but not for harms.

Allocation concealment

- Low risk of bias. Allocation was controlled by a central and independent randomisation units, opaque, sealed, and serially numbered envelopes; or similar so that intervention allocations could not have been foreseen in advance of, or, during enrolment.
- Uncertain risk of bias. The trial was described as randomised, but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or enrolment.
- High risk of bias, if the allocation sequence was known to the investigators who assigned participants, or if the study was quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits but not for harms.

Blinding of participants, personnel, and outcome assessors

- Low risk of bias. Blinding was performed adequately, or the outcome measurement is not likely to be influenced by lack of blinding.
- Uncertain risk of bias. There is insufficient information to assess whether the type of blinding used is likely to induce bias on the estimate of effect).
- High risk of bias. There is no blinding or incomplete blinding, and the outcome or the outcome measurement is likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias. The underlying reasons for missingness are unlikely to make treatment effects departure from plausible values, or proper methods have been employed to handle missing data.
- Uncertain risk of bias. There is insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data is likely to induce bias on the estimate of effect.
- High risk of bias. The crude estimate of effects (eg, complete case estimate) will clearly be biased due to the underlying reasons for missingness, and the methods used to handle missing data are unsatisfactory.

Selective outcome reporting

- Low risk of bias. The trial protocol is available and all of the trial's pre-specified outcomes that are of interest in the review have been reported or similar.
- Uncertain risk of bias. There is insufficient information to assess whether the magnitude and direction of the observed effect is related to selective outcome reporting.
- High risk of bias. Not all of the trial's pre-specified primary outcomes have been reported or similar.

Other risk of bias

- Low risk of bias (the trial appears to be free of other components that could put it at risk of bias).
- Uncertain risk of bias (the trial may or may not be free of other components that could put it at risk of bias).
- High risk of bias (there are other factors in the trial that could put it at risk of bias, eg, for-profit involvement (eg, sponsor bias), authors have conducted trials on the same topic (academic bias) etc.).

If the risk of bias in a trial is judged as low in all the above domains, the trial will fall into the category of "low risk of bias" group. If the risk of bias is judged to be "uncertain" or "high", then the trial will fall into the group of trials with "high risk of bias".
All the above bias risk domains will be assessed independently by two authors. Disagreements between the authors will be resolved by discussion and arbitrated with a third author.

Measures of treatment effect

Dichotomous data

The relative risks with 95% confidence intervals (CI) will be calculated by the fixed-effect model (DeMets 1987) and the random-effects model (DerSimonian 1986), and where relevant, as risk difference (RD) and number needed to treat (NNT). We will report both models in case of disagreement between them. Otherwise, we will only report the fixed-effect model.

Continuous data

Mean differences with 95% CI will be calculated for continuous outcome measures (DeMets 1987). The standardised mean difference (SMD) will be used to combine trials that measure the same outcome, but have used different methods.

Unit of analysis issues

We will analyse aggregate data from the intervention groups of randomised clinical trials. In case no randomised clinical trials are identified, we will summarise the results of published studies in the 'Discussion' section. The summary will be conceived with the purpose of guiding the researchers who wish to conduct randomised clinical trials on the effect of chelating agents for Wilson's disease.

If our searches identify any cross-over trials, we will take only data from the first trial period into consideration.

Dealing with missing data

All analyses will be performed according to the intention-to-treat method, using the last reported observed response ('carry forward'), and including all participants irrespective of compliance or follow-up. In addition, 'worst-case scenario' and 'best-case scenario' analyses will be performed, and participants with missing data will be considered as treatment failures or treatment successes. Also, we will impute the mean as a third analysis method.

Assessment of heterogeneity

Statistical heterogeneity will be assessed by inspection of graphical presentations ('forest plot') (Egger 1997) and by calculating both the I-square and the Chi-square tests statistic (Higgins 2009).

Assessment of reporting biases

Funnel plot asymmetry will be used to assess the existence of bias if there are a minimum number of ten trials (Egger 1997).

Data synthesis

We will attempt a meta-analysis where there are sufficient data of suitable type, using RevMan 5 (RevMan 2008). In the event that there are too few clinically homogeneous trials for us to be able to

perform a meta-analysis, we will present a narrative synthesis of the data (RevMan 2008).

Subgroup analysis and investigation of heterogeneity

If possible, we will perform subgroup analyses in this review according to:

- Risk of bias. Trials with low risk of bias compared to trials with high risk of bias.
- Severity of liver disease at entry.
- Severity of neurological symptoms at entry.

Sensitivity analysis

We will utilise the trial sequential analysis to test the robustness of our findings (Wetterslev 2008). The required information size will be calculated based on the event proportion in the control group, a relative risk reduction of 10%, 20%, and 30%, an alpha of 5%, a beta of 20%, and the diversity in the meta-analysis (Wetterslev 2008).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

1 Search Strategies

Database	Time span of search	Time span of search
Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage.	Wilson* AND (chelat* OR copper OR penicillamine OR trientine OR 'ammonium tetrathiomolybdate' OR zinc)
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Latest issue.	#1 MeSH descriptor Hepatolenticular Degeneration explode all trees #2 wilson's disease #3 (#1 OR #2) #4 MeSH descriptor Chelating Agents explode all trees #5 MeSH descriptor Chelation Therapy explode all trees #6 (chelat* OR copper OR penicillamine OR trientine OR 'ammonium tetrathiomolybdate' OR zinc) #7 (#4 OR #5 OR #6) #8 (#3 AND #7) 25
MEDLINE (Ovid SP)	1950 to the date of search.	1. exp Hepatolenticular Degeneration/ 2. wilson's disease.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 3. 1 or 2 4. exp Chelating Agents/ 5. exp Chelation Therapy/ 6. (chelat* or copper or penicillamine or trientine or 'ammonium tetrathiomolybdate' or zinc).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 7. 4 or 5 or 6 8. 3 and 7 9. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 10. 8 and 9
EMBASE (Ovid SP)	1980 to the date of search.	1. exp Wilson disease/ 2. wilson's disease.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

(*Continued*)

		3. 1 or 2 4. exp chelating agent/ 5. exp chelation therapy/ 6. (chelat* or copper or penicillamine or trientine or 'ammonium tetrathiomolybdate' or zinc).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 7. 4 or 5 or 6 8. 3 and 7 9. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 10. 8 and 9
Science Citation Index Expanded (http://apps.isiknowledge.com)	1900 to the date of search.	# 5 #4 AND #3 # 4 TS=(random* or blind* or placebo* or meta-analysis) # 3 #2 AND #1 # 2 TS=(chelat* or copper or penicillamine or trientine or 'ammonium tetrathiomolybdate' or zinc) # 1 TS=(Wilson's disease)

CONTRIBUTIONS OF AUTHORS

All authors contributed to the draft version of the protocol.

DECLARATIONS OF INTEREST

None known.

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External sources

- No sources of support supplied