Oral zinc sulphate for Wilson’s disease

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SUMMARY After initial promotion of copper excretion with D-penicillamine, the effect of oral zinc sulphate (3 × 150 mg/day, loading dose; 3 × 100 mg/day, maintenance dose) in two children with clinically stable Wilson’s disease was evaluated after completion of three years’ treatment. The course, judged by clinical, biochemical, and histological parameters was satisfactory in both. The urinary copper concentration reverted to less than 1-26 μmol/24 hours; and the serum copper concentration decreased further during zinc sulphate treatment. In one child the rise in 24 hour urinary copper excretion observed after a challenge dose of D-penicillamine (±20 mg/kg) remained constant throughout the period of observation while the liver copper content fell from 1460 μg/g dry weight to 890 μg/g dry weight. In the other patient, however, the liver copper content as well as the 24 hour urinary copper excretion increased after D-penicillamine challenge during the third year of treatment.

We conclude that zinc sulphate is a low toxic and well tolerated alternative for D-penicillamine. The dosage depends, however, on individual factors not yet well understood, and we recommend restriction of its use to patients who do not tolerate D-penicillamine well. We suggest monitoring of treatment with yearly D-penicillamine challenge and a liver biopsy if liver function deteriorates.

The current treatment for Wilson’s disease is restriction of copper intake and promotion of urinary copper excretion by an oral copper chelating agent, D-penicillamine. Side effects and toxic reactions are frequently observed and are severe enough in a few instances to necessitate the stopping of treatment. Moreover, non-compliance is the major problem with this life long treatment and may be partially due to an aversion to the taste of D-penicillamine.

A different treatment approach—that is, inhibition of the gastrointestinal absorption of copper by the administration of a copper binding agent has been considered. Substances such as carbacrylamide and potassium sulphide, however, have been unsuccessful in maintaining negative copper balance.

The antagonistic action of zinc on copper absorption had already been known for years in veterinary medicine when, in 1961, Schouwink described the same effect in two patients with Wilson’s disease: one of them has been treated successfully for the past 25 years with zinc. The observation that large doses of zinc can inhibit copper absorption was further confirmed in sickle cell patients and recently in a well controlled balance study of five patients with Wilson’s disease. Zinc sulphate may thus be considered as a low toxic and safe alternative to the classic treatment with D-penicillamine in patients unable to tolerate the latter drug. We describe our experience with two such children, treated for three years with zinc sulphate after initially promoting urinary copper excretion with D-penicillamine.

Patients and methods

The two children were aged 3 and 5 years when D-penicillamine treatment was started and 4 and 8 years, respectively, when zinc sulphate was introduced. They were in a stable clinical condition—Kayser-Fleischer rings, neurologic symptoms, jaundice and portal hypertension were absent. Patient 2 presented initially with a chronic active hepatitis-like syndrome without splenomegaly, while patient 1 was an asymptomatic sibling of a patient known to have Wilson’s disease. On hospital admission both patients had raised transaminases. Criteria for diagnosis were: liver copper value greater than 325
μg/g dry weight, urinary copper excretion greater than 1·26 μmol/24 hours before treatment, ceruloplasmin concentration less than 200 mg/l, abnormal radiocopper kinetics (no incorporation of 64Cu in ceruloplasmin), and family history in patient 1.

Serum and 24 hour urine for zinc and copper assays as well as liver biopsy specimens were collected in metal free containers. All metal analyses were performed in duplicate by atomic absorption spectrophotometry. The intravenous radiocopper test was performed according to a modification of a previously described protocol.8 64Cu (half life 12·7 hours) was used at a dose of 0·03 mCi (6 millirem). The radiocopper studies were approved by the hospital ethical committee as the dose was low, the half life of the isotope short, and the disease potentially fatal. Serum liver function tests were carried out at intervals of approximately three months. Liver biopsies were examined with transmission electron microscopy.

The zinc treatment regimen was oral zinc sulphate with the meals—3 × 150 mg/day initially, followed by a maintenance dose of 3 × 100 mg/day (Zn SO4.7H2O corresponding to 3X 34 and 3X 22·5 mg/day of elemental zinc, respectively). During challenge tests with D-penicillamine (20 mg/kg), zinc treatment was stopped for three days beforehand.

Results

The Figure shows the course of serum copper values and 24 hour urinary copper excretion throughout treatment in both patients. Initially serum copper fell after D-penicillamine to 4·4 μmol/l and 3 μmol/l respectively and decreased further during oral zinc sulphate treatment. 24 hour urinary copper excretion was raised at diagnosis. It increased (as expected) during D-penicillamine treatment, but after this was stopped returned to normal values for patients with liver diseases (less than 1·26 μmol/24 hours) when the oral zinc sulphate regimen was reinstituted.

Fig. 1  Serum copper and 24 hour urinary copper excretion during D-penicillamine and zinc sulphate treatment in two patients with Wilson's disease.

Conversion—traditional units to SI: Serum copper 1 μg/dl = 0·157 μmol/l; urinary copper 1 μg/24 hours = 0·0157 μmol/24 hours.
The liver function tests (for example, transaminases) became normal after the initial treatment with D-penicillamine and have remained so for the past three years on zinc sulphate treatment. The Table shows the effect of a challenge dose of D-penicillamine on 24 hour urinary copper excretion after 3, 15, 27, and 39 months of zinc treatment.

The resolution rate of intravenously administered $^{64}$Cu from the plasma in both patients measured at yearly intervals after the start of zinc treatment, showed little change and the curves obtained were consistent with the absence of copper accumulation.

Light microscopy initially showed a diffuse steatosis in both patients and a perportal inflammatory infiltrate with perilobular fibrosis and hepatocellular necrosis in patient 2. Three years after zinc sulphate treatment the liver histology was greatly improved and in both patients virtually normal. The ultrastructural changes (electron microscopy) were still characterised by the presence of heterogeneous multivesiculated inclusion bodies (lysosomes?) in the hepatocytes. The mitochondria showed varied shapes and sizes with deterioration of a substantial part of the cristae.

The liver copper content, which was 350 μg/g dry weight after initial treatment with D-penicillamine in patient 2, rose to 1050 μg/g dry weight after three years of zinc sulphate therapy. In patient 1 the liver copper content decreased from 1460 μg/g dry weight at diagnosis to 890 μg/g dry weight.

No side effects were observed.

Discussion

There is now good evidence that long term zinc sulphate treatment can maintain neutral or negative copper balance in patients with clinically stable Wilson's disease. Recently, Brewer et al. reported that pharmacological doses of oral zinc promoted the faecal excretion of copper in patients with Wilson's disease treated with D-penicillamine, provided that the previously depleted total body zinc was restored. This view is supported by the normal liver function tests, by the reversion of the urinary copper excretion to normal, and by the maintenance of a low serum copper concentration during three years of zinc sulphate treatment in both children described here. The small but consistent rise in urinary copper excretion after a challenge dose of D-penicillamine in patient 1 leads to the same conclusion. This is further confirmed by the histological course of the disease in both patients and by the determination of the liver copper content in patient 1.

The increase in liver copper content observed in patient 2, is however, disturbing, and the absence of a concomitant increase in the transaminases values remains unexplained. This rise may be due to a sampling error in the initial biopsy: in fact, such errors are not unusual in fibrotic tissue. On the other hand, the dose of zinc sulphate may not have been large enough to prevent some reaccumulation of copper in the liver. That this could have occurred at the end of three years' treatment in patient 2 may be deduced from the rise observed in 24 hour urinary copper excretion after the challenge dose of D-penicillamine. It is possible that zinc promotes the synthesis of metallothionein, not only in the intestinal but also in the liver cells. Metallothionein is known to have a higher affinity for copper than for zinc. Any copper escaping the blocking effect of zinc on absorption will probably be bound to liver metallothionein and this mechanism may temporarily protect the tissue against the toxic effect of free copper, explaining the absence of symptoms observed. The quantity of zinc required to block the copper absorption adequately has thus to be determined individually.

No previous data on the liver copper content of patients with Wilson's disease treated with zinc sulphate are known to us. Nevertheless, since 1957 zinc sulphate has been shown to maintain a negative copper balance and a satisfactory clinical condition in several patients in the Netherlands. It can therefore be considered as a low toxic, low cost, and safe alternative to D-penicillamine, provided the dosage is adjusted to individual needs. The effect of a low copper diet and of a specific zinc dose on the individual copper absorption are still poorly understood at present. As long as zinc sulphate has not been proved effective in all patients, we suggest that it is prescribed only if D-penicillamine is either not tolerated or not available. We recommend a challenge with a test dose of D-penicillamine every 12 months and that the maintenance dose of zinc sulphate should be adjusted according to the result. In case of doubt a liver biopsy is indicated. As yet there is no clinical experience with zinc treatment in acutely ill patients with Wilson's disease.
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We thank Mrs Ingrid Luijendijk for the copper and zinc determinations, Dr C J A Van den Hamer for the intravenous radiocopper-test and Mrs Ingrid Bracke for secretarial help. We also thank Professor J Fernandes for reviewing the manuscript, and Mrs E Konig for reviewing the language. This study was supported by the Sophia Foundation for Medical Research.

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Arch Dis Child 1985 60: 656-659
doi: 10.1136/adc.60.7.656

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