3. Chaussy C, Schmiedt E, Jocham D, et al. Extracorporeal shock-wave lithotripsy (ESWL) for treatment of urolithiasis. Urology 1984; 23:59–66.

4. Drach GW, Dretler S, Fair W, et al. Report of the United States Cooperative Study of extracorporeal shock-wave lithotripsy. J Urol 1986; 135:1127–1133.

5. Schoenfield LJ, Lachin JM, et al. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: The National Cooperative Gallstones Study: a controlled trial of efficacy and safety. Ann Intern Med 1981; 95:257–282.

6. Erlinger S, Le Go A, Husson JM, et al. Franco-Belgian cooperative study of ursodeoxycholic acid in the medical dissolution of gallstones: a double-blind, randomized, dose-response study, and comparison with chenodeoxycholic acid. Hepatology 1984; 4:308–314.

7. Allen MJ, Borody TJ, Bugliosi TF, et al. Rapid dissolution of gallstones by methyl tert-butyl ether: preliminary observations. N Engl J Med 1985; 312:217–220.

8. Charig CR, Webb DR, Payne SR, et al. Comparison of treatment of renal calculi by open surgery, percutaneous nephrolithotomy, and extracorporeal shockwave lithotripsy. Br J Med 1986; 292:877–879.

ZINC THERAPY OF WILSON'S DISEASE: TWO VIEWS

ABSTRACT

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.

COMMENTS

The authors report clinically satisfactory control of Wilson's disease in two children on zinc sulfate therapy for 3 years each, but raise concerns about an increasing hepatic copper in one patient. This patient also showed an increasing urinary copper response to penicillamine challenge. Based on only these two patients, who were given a low dose of zinc which they took with food, the authors then develop rather sweeping conclusions that the dosage of zinc depends on individual factors not well understood, and that zinc should be restricted to patients not tolerating penicillamine.

Our own experience is based on 39 patients treated with zinc, the longest for 5 years, with an average of about 2.5 years (1–4). Our standard dose is 50 mg elemental zinc (as the acetate salt) taken three times per day, avoiding food by an hour before and after each dose. In contrast, the authors used about 23 mg elemental zinc (as the sulfate) three times per day, taken *with* meals. This dose is lower than has been proven adequate by either ourselves or the Hoogenraad Group (5), who have also been using zinc for the maintenance therapy of Wilson's disease. However, my main criticism of the authors zinc regimen is that they gave the zinc with food. We (6) and others (7) have shown that this greatly reduces zinc's effectiveness. The use of the acetate salt makes it feasible to give zinc in the absence of food, since it causes much less gastric irritation than the sulfate salt.

The authors monitored efficacy by evaluating control of symptoms, liver function tests, serum copper, urine copper levels in the absence and presence of penicillamine, hepatic copper levels and morphology and an IV^{64} copper ^{64}Cu procedure. We monitor efficacy by most of these techniques (no IV ^{64}Cu procedure) plus copper balance, ^{64}Cu uptake into blood after an oral dose, level of nonceruloplasmin plasma copper, slit lamp exam, quantitative neurological exam and a variety of other specialized examinations. Copper balance is a research procedure and is thus not feasible in the usual clinical setting, but it is the standard by which we have validated the other monitoring procedures. ^{64}Cu uptake is very useful because the mechanism of zinc action is blockade of intestinal uptake of copper, and with a fully effective dose of zinc, the blood ^{64}Cu peak will be less than 1% of the administered dose (4). We have found the 24-hr urinary excretion of copper to be more useful than urine copper after penicillamine challenge. In the absence of penicillamine treatment, the urinary excretion of copper reflects the body load of excess copper much as glycosuria reflects excess glucose in a diabetic patient. In well-decoppered patients, this value should be below 100 μ per 24 hr. Trends upward over time suggest inadequate control. Measuring the copper in urine accurately, particularly in the normal or near-normal range, requires a good atomic absorption spectrophotometer. (We use an Instrumentation Laboratory Model 451, which even in the flame mode has this capability.) The problems with using the penicillamine challenge procedure to monitor patients on zinc includes the variability of this procedure, but more importantly we have seen the values go downward over time in patients who were well decoppered in the first place while all other parameters indicate no change in copper status. We suspect that in zinc-loaded patients, zinc competes with copper for binding to the

penicillamine. Stopping zinc even for 2 weeks prior to the test has not remedied this problem.

Another simple and useful variable to follow is the nonceruloplasmin plasma copper. If one subtracts the ceruloplasmin copper from total plasma copper, one obtains the value for the potentially toxic copper. We like to see this value kept below 25 μg per dl. Trends upward suggest loss of control. Hepatic copper as assessed by biopsy is a method for evaluating control of copper accumulation by anticopper therapy over a longer time span. Our experience in well-decoppered patients on zinc therapy is very good (Brewer, G. J. et al., Clin. Res. 1985; 33:871A, Abstract). In 10 such patients biopsied at the beginning and after 12 to 20 months of therapy, no patient showed reaccumulation of hepatic copper (mean before was 218 μg per gm dry weight, while the after therapy mean was 200 μg per gm dry weight).

Summarizing our efficacy experience with patients on a maintenance dose of 50 mg of zinc three times per day, we have seen excellent control of copper balance, hepatic copper levels, prevention of redevelopment of Kayser-Fleischer rings and no redevelopment of symptoms. On three occasions, we have noted increasing urinary copper and nonceruloplasmin plasma copper in particular patients. In each case, we found a compliance problem with the patient taking the medication.

My assessment of the authors results in these two patients is that the patients have done well considering the low dose and administration of zinc with meals. Both patients showed a reduction of total serum copper, which means, if ceruloplasmin levels did not change, that nonceruloplasmin plasma copper came under good control. Urinary copper was also well controlled in both patients (except for one high value in both patients at about 3 years). It is difficult to interpret the one unusually high penicillamine cupruresis value in Patient 2 because of the problem with this procedure already mentioned. The higher hepatic copper value in this same patient suggests the need for a rebiopsy. On two occasions, we have seen differences of 400 to 500 μg copper per gm dry weight from different liver biopsy samples from the same patient, and rebiopsy in both cases confirmed one of the values, indicating that indeed the Wilson's disease liver can on occasion by "patchy" with respect to copper. The addition of an oral ^{64}Cu uptake procedure to this patient's evaluation at this same point would have told us much about adequacy of control.

Zinc acetate for the treatment of Wilson's disease has been designated an orphan treatment by the U.S. FDA, and has been adopted for development by the Lemmon Company. We anticipate possible marketing (pending FDA approval) by 1987. The dose I recommend, at least for the present, is 50 mg of elemental zinc, three times per day, avoiding food by 1 hr. The minimal monitoring procedures for patients on maintenance therapy should include 24-hr urine copper, nonceruloplasmin plasma cooper, oral ^{64}Cu uptake and appropriate clinical studies. Assessment of hepatic copper can also be used, but should not be necessary on a routine basis. Our present experience indicates that all Wilson's disease patients can be safely maintained on zinc therapy, if they take an adequate dose away from meals.

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REFERENCES

1. Brewer GJ, Hill GM, Prasad AS, et al. A new treatment for Wilson's disease. Ann Intern Med 1983; 99:314–320.
2. Brewer GJ, Hill GM, Dick RD, et al. Interactions of trace elements: clinical significance. J Am Coll Nutr 1985; 4:33–38.
3. Brewer GJ. Zinc therapy for the treatment of Wilson's disease. Generics 1985; 1:54–55.
4. Hill GM, Brewer GJ, Juni JE, et al. Treatment of Wilson's disease with zinc. II. Validation of oral [64]copper with copper balance. Am J Med Sci 1986 (in press).
5. Hoogenraad TU, Van Den Hamer CJA. Three years of continuous oral zinc therapy in 4 patients with Wilson's disease. Acta Neurol Scand 1983; 67:356–364.
6. Oelshlegel FJ, Brewer GJ. Absorption of pharmacological doses of zinc. In: Prasad AS, Brewer GJ, eds. Zinc metabolism: current aspects in health and disease. New York: Alan R. Liss, 1977: 299–311.
7. Pecoud A, Dozel P, Schelling JL. The effect of foodstuffs on the absorption of zinc sulfate. Clin Pharmacol Ther 1975; 17:469.

COMMENTS

Evaluating this paper, which concludes that zinc sulfate is an alternative treatment to penicillamine in Wilson's disease, requires a comparison of the natural and pharmacologically modified histories of Wilson's disease.

Wilson's disease represents chronic copper intoxication in man, primarily affecting the liver and brain. It occurs only in individuals who inherit an abnormal pair of specific, autosomal, recessive genes. From 1912, when Wilson first described the syndrome (1) through 1956, when Walshe suggested that D-penicillamine might be effective therapy (2), the disease was always fatal. Patients died of either hepatic or cerebral involvement, usually after torturous years of hepatic, neurologic and psychiatric symptoms. Unlike most inborn errors of metabolism, symptoms of the disease never appear before 6 years of age, are unusual before adolescence, and, rarely, do not appear for more than 40 years (3).

Penicillamine, the dimethyl derivative of cysteine, revolutionized the treatment and course of this disease. Severely ill patients were often restored to completely normal health. Patients in whom the diagnosis of Wilson's disease was made while they were still asymptomatic remained so indefinitely if they continuously took 1 gm or so of penicillamine daily.

Furthermore, penicillamine was not very toxic. In our personal experience, a toxic reaction requiring withdrawal of penicillamine, most commonly for proteinuria, occurred in about 5% of patients. For such patients triethylene tetramine dihydrochloride (Trien® or Cuprid®), also introduced by Walshe in 1970, has proven to be as effective therapeutically as penicillamine (4). Trien® was approved for Wilson's disease by FDA in 1985.

The paper of Caillie-Bertrand et al. provides little justification for the therapeutic use of zinc in Wilson's

disease. Indeed, there was no apparent clinical indication for its use in the two asymptomatic children with the disease that they report. Both were "clinically stable" with no indication of toxicity to penicillamine after 1 and 3 years of treatment, respectively. Apparently, there were no changes in their clinical condition during 3 years of zinc treatment. Both were asymptomatic when zinc was started and might well have remained so for years without any treatment. Although zinc treatment was accompanied by a fall in hepatic copper concentration of one patient, from 1,460 μg per gm dry weight to 890, that of the other rose from 350 to 1,050 μg per gm dry weight. This is faint praise.

It is well established that zinc, usually in about twice the dosage used by these authors, can inhibit the gastrointestinal absorption of copper (5). It has as yet not been shown that this action is accompanied by a decrease in the copper concentrations of either the liver or the brain.

A controlled double-blind study of the therapeutic role of zinc in Wilson's disease can almost certainly not now be performed. It is difficult to see how a patient with an unequivocal diagnosis of this lethal disorder can ethically be denied treatment with penicillamine or Trien® for the length of time necessary to determine whether zinc therapy is effective. If the patient is asymptomatic, and remains so, how and when can one conclude that zinc was beneficial? Whether asymptomatic or symptomatic, particularly in the presence of hepatic dysfunction, the escalation of the disease to fulminant hepatitis is usually irreversible and is often rapidly fatal.

These authors classify zinc as being of low toxicity. Both copper and zinc are essential, heavy metals of virtually identical atomic weight which are present in trace quantities in metalloproteins and enzymes almost exclusively as prosthetic elements. Since the two metals are so much alike chemically, and biologically, and since it is known that copper is toxic, can it be assumed that years of administering zinc in ten or more times the daily nutritional requirement, the zinc will be nontoxic, or only minimally so?

Except for the patient with Wilson's disease who has had no beneficial response to a long course of penicillamine therapy or a significant, irreversible reaction to both penicillamine and Trien®, zinc has no place in the treatment of Wilson's disease. Readers who question this recommendation should ask themselves how they would want their own children with Wilson's disease to be treated.

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REFERENCES

1. Wilson SAK. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. Brain 1912; 34:295-507.
2. Walshe JM. Penicillamine. A new oral therapy for Wilson's disease. Amer J Med 1956; 21:487-495.
3. Scheinberg IH, Sternlieb I. Wilson's disease. Philadelphia, Pennsylvania: W. B. Saunders Co., 1984.
4. Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. Lancet 1982; 1:643-647.
5. Van den Hamer CJA, Hoogenraad TU. ⁶⁴Cu loading tests for monitoring zinc therapy in Wilson's diseae. Trace Elements in Med 1984; 1:84-87.

MEMBRANE POTENTIAL AND HEPATIC UPTAKE: ANOTHER RULE OF THE GAME

Edmondson JW, Miller BA and Lumeng L. Effect of glucagon on hepatic taurocholate uptake: relationship to membrane potential. Am. J. Physiol. 1985; 249 (Gastrointest. Liver Physiol. 12):G427-G433.

ABSTRACT

Since glucagon can hyperpolarize hepatic plasma membrane and stimulate biliary bile acid secretion in vitro, we studied the effect of glucagon on taurocholate uptake and its relationship to plasma membrane potential in isolated rat hepatocytes. [^{14}C]Taurocholate uptake was linear through 1 min and contained a saturable sodium-dependent and a nonsaturable sodium-independent component, K_m of taurocholate uptake by the sodium-dependent system was 18.4 μM. Hill coefficient for Na^+ was 2.59 and for taurocholate was 1.1, suggesting that the stoichiometry is 2 Na^+:1 bile acid. Stimulation of taurocholate uptake by glucagon was limited to the sodium-dependent component, detected within 5 min of hormone exposure, and was maximum at 30 min. Glucagon, from 10^{-8} to 10^{-5} M, stimulated taurocholate uptake and hyperpolarized concurrently the plasma membrane potential. Because valinomycin produced a dose-related depolarization of plasma membrane potential, this agent was used to counteract the effects of glucagon. With 10^{-6} M glucagon, valinomycin (10^{-10} M) depolarized membrane potential from -35.50 to -28.00 mV and inhibited taurocholate uptake from 60% above the control rate to 5% below. These data strongly suggest that taurocholate uptake by isolated hepatocytes is an electrogenic process, and its stimulation by glucagon may be mediated by changes in plasma membrane potential.

COMMENTS

The complex process by which liver takes up, stores and excretes into the bile exogenous and endogenous compounds has been addressed in the past by several investigators. Bile acids are a composite class of substances with several important characteristics. One of the critical steps in their metabolism is the uptake occurring at the sinusoidal-basolateral plasma membrane. In spite of the large number of investigations which deal with bile acids, some of the key issues in their metabolism are still unclear. Among these is the point Edmundson and coworkers address in this article, i.e., does the uptake process of taurocholate occur electrogenically? In this investigation, freshly isolated rat hepatocytes were measured for taurocholate uptake after modification of the