ORAL ZINC SULPHATE IN RHEUMATOID ARTHRITIS

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Summary A preliminary trial of oral zinc supplementation was conducted in twenty-four patients with chronic, refractory rheumatoid arthritis. Zinc sulphate (220 mg three times daily) or placebo capsules of identical appearance were added to pre-existing therapy for 12 wk. This double-blind trial was followed by an open 12-wk period when all subjects took zinc. During the double-blind phase, zinc-treated patients fared better than controls with regard to joint swelling, morning stiffness, walking time, and the patient's own impression of overall disease activity. The indices and joint tenderness also improved with zinc treatment in both groups of subjects during the second 12-wk period. These encouraging results indicate that oral zinc sulphate deserves further study in patients with active rheumatoid arthritis.

Introduction

ACTIVE rheumatoid arthritis presents a major therapeutic challenge to every clinician. The disease may be devastating and accepted therapeutic agents are too often ineffective. As a result, new drugs of high potential toxicity have been introduced and used widely in attempts to arrest the progression of this disease. Safer and more effective therapy is badly needed.

The present trial was begun in hopes that patients with rheumatoid arthritis might benefit from oral zinc sulphate, an agent that has been safely used to promote healing in man. The study is based on the hypothesis that ionic zinc is in some way essential for the normal synovium, and that local zinc levels are depleted in rheumatoid synovitis. Repletion of synovial zinc may then facilitate host resistance to the disease.

Low levels of serum-zinc provide the best evidence of zinc depletion in rheumatoid arthritis. In sixty-eight patients Niedermeier and Griggs[1] found a mean serum-zinc level of 73 μg/dl which was significantly less ($P<0.001$) than their control mean of 115 μg/dl. This difference was recently confirmed in a larger study correlating low serum-zinc concentrations with decreased bone density in this disease.[2] Although the underlying mechanism is not known, these large series suggest that zinc depletion is common in rheumatoid patients.

The low serum-histidine levels which are characteristic of rheumatoid arthritis[3] may be relevant here, since zinc and histidine are closely linked in normal metabolism: most of the "direct reacting" zinc in plasma is complexed to this aminoacid;[4] zinc ions in metalloenzymes (such as alkaline phosphatase) may be coordinated with histidine residues;[5] and complexing with histidine and other absorbable chelating agents is known to enhance the gastrointestinal absorption of ionic zinc.[6] It is plausible, then, that low levels of serum-histidine are either the cause or the effect of abnormal zinc metabolism in rheumatoid patients. A possible parallel can be found in zinc-deficient chickens which suffer from a disabling leg deformity responsive to supplementation with either zinc or histidine.[7]

It is similarly possible that the demonstrated effectiveness of oral D-penicillamine against rheumatoid arthritis[8] may reflect the effects of this agent on zinc metabolism. A little-known property of penicillamine is its ability to promote gastrointestinal absorption of zinc.[9] Urinary zinc excretion also rises, but the gastrointestinal effect predominates, leading to a positive zinc balance. The ensuing increase in tissue zinc could be responsible for the clinical improvement in rheumatoid patients receiving penicillamine.

If oral zinc supplementation can lead to increased levels in the synovium, a therapeutic effect would be predicted from the known anti-inflammatory properties of zinc ions. These effects have been repeatedly demonstrated in vitro including stabilisation of lysosomal membranes,[10] inhibition of prostaglandin synthesis,[11] interference with the complement system,[12] and impairment of macrophage function.[13] In view of these observations, it is logical to expect that rheumatoid inflammation will be less restrained and therefore more active when zinc levels are low. Zinc supplementation would reverse this process, inhibit the inflammatory response, and thereby ameliorate the effects of the disease.

Oral zinc sulphate (220 mg three times daily) has been used widely to treat chronic ulceration of the skin and to promote healing of surgical wounds.[14 15] Although the use of zinc for these conditions is controversial, it is well established that this agent has very little short-term toxicity. In view of its apparent safety and for the reasons discussed above, we undertook a double-blind trial of oral zinc sulphate *vs.* placebo in patients with chronic, active rheumatoid arthritis.

Methods

Twenty-four patients with definite or classical rheumatoid arthritis[16] agreed to participate in the trial. All patients had active disease despite conventional therapy which included salicylates in 23, prednisone in 11, and maintenance gold injections in 5 (most of the other patients had previously received gold therapy). Additional agents included indomethacin (2) chloroquine (2), chlorambucil (1), and oxyphenbutazone (1). The well established refractory nature of the disease was reflected in the duration of the arthritis (11·3±6·7 years) (mean±S.D.) and in the average number of joints that were swollen, tender, or both (22·8±7·1). The average age was 54·3±11·2 years.

Twenty patients were studied by me at the University of Washington, Seattle, the other four by Dr Robert Levy in his private rheumatology practice in Olympia, Washington. Each was fully informed of the experimental design and alerted to the possible side-effects of zinc sulphate. Return visits were at 2, 4, 8, 12, 16, 20, and 24 wks. All patients were asked to continue their previous medication without change, but to take three additional capsules daily. The capsules, containing either zinc sulphate (220 mg) or a placebo, were of identical appearance and were prepared and coded under the direction of Dr Elmer Plein, department of pharmacy, University of Washington. The patients were randomly allocated in an undisclosed sequence to receive either zinc sulphate (group Z) or placebo (group P). These two groups did not differ significantly from each other in mean age, disease duration, or number of involved joints. After 12 wk, the code was broken and the study continued for a 12-wk period during which all patients received zinc sulphate (220 mg three times daily) as commercial 'Orazinc R' capsules (Mericon Industries, Peoria, Illinois).

At the first visit, we examined sixty-eight joints, recording scores for swelling (0 to 4) and for tenderness (0 to 4) in each joint. Morning stiffness was scored according to the number of

MEAN SCORES (± S.E.M.) OF CLINICAL INDICES AT EACH EVALUATION

Index	Group	Week 0	2	4	8	12	16	20	24
Swelling	Z	27±3	22±4†	22±2*	20±3†	20±3	17±2	14±2	17±4
	P	14±2	14±2	14±3	15±3	13±3	11±3	10±2	9±2
Tenderness	Z	28±5	26±4	27±4	29±4	24±5	18±3	15±4	13±4
	P	28±5	29±7	26±6	27±7	29±9	23±8	22±9	20±8
Stiffness	Z	4·0±0·4	3·1±0·7	2·4±0·6*	2·5±0·8*	3·0±0·8	2·7±0·8	3·2±0·7	1·8±0·7
	P	3·5±0·4	3·0±0·5	3·4±0·5	3·4±0·6	3·6±0·5	2·8±0·5	2·7±0·6	2·7±0·5
Grip	Z	100±16	110±17	114±22	110±17	98±14	105±16	103±14	103±14
	P	85±12	88±10	84±12	82±12	84±11	79±9	82±8	88±12
50ft walk	Z	17±1	15±1	14±1*	14±1*	14±1	15±1	15±1	14±1
	P	16±2	15±1	16±2	15±1	15±2	15±2	15±2	14±1
Condition	Z	3·3±0·2	3·7±0·2	3·5±0·2*	3·5±0·3	3·1±0·3	3·7±0·3	3·6±0·4	3·6±0·2
	P	3·1±0·1	3·3±0·2	2·6±0·3	2·8±0·2	3·2±0·2	3·3±0·2	3·3±0·1	3·6±0·3
Since last visit	Z	No data	3·8±0·2	3·2±0·2	3·6±0·3*	3·1±0·4	3·1±0·4	3·4±0·3	3·7±0·2
	P	No data	3·3±0·3	3·0±0·3	3·0±0·2	3·0±0·2	3·5±0·2	3·5±0·2	3·4±0·3

Z=zinc sulphate 0-24 wk; P=placebo 0-12 wk, zinc sulphate 12-24 wk.
* $P<0.05$, † $P<0.01$, probabilities based on t tests of change in group Z v. change in group P where change is determined with reference to week 0 (except for change "since last visit"). Groups Z and P were not statistically compared in weeks 16-24 since all patients were treated alike.

hours of stiffness, ½ h=1, ½ to 1 h=2, 1 to 1½ h=3, 1½ to 2 h=4, 2 h or more=5.[17] Grip strength was measured using a rolled sphygmomanometer cuff, starting at 20 mm Hg. Those able to walk 50 ft in under 30 sec were timed over the distance. All patients assessed their own overall condition using a scale of 1 to 5: very poor=1, poor=2, average=3, good=4, very good=5, and gave their impression of the change since the previous visit: much worse=1, worse=2, the same=3, better=4, much better=5.

We kept a tally on all medications and possible side-effects, including headache, rash, change in appetite, abdominal pains or discomfort, nausea, vomiting, change in bowel habits, or any other new symptom.

Hæmatocrit, white blood-cell (W.B.C.) count, and erythrocyte sedimentation rate (E.S.R.) (Westergren method) were also determined at each visit.

At 0, 12, and 24 wk, urinalysis was done and blood drawn for serum assay of zinc,[18] histidine,[19] rheumatoid factor,[20] and urate.[21] Sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, bilirubin, alkaline phosphatase, glucose, creatinine, and urea were also determined in the same specimens by standard autoanalyser techniques.

Both conventional and xerographic radiographs of the hands were taken at 0, 12, and 24 wk, by courtesy of Dr Rosalind Troupin, department of radiology, University of Washington.

Results

Patients taking zinc sulphate fared better in all clinical parameters than did patients receiving placebo over the 12 wk of the double-blind trial. These trends reached statistical significance at one or more evaluation intervals for joint swelling, morning stiffness, walking time, and the patients' impressions of both "overall condition" and "change since the previous visit". During the second 12 wk, group Z had continued improvement in these parameters, as well as an impressive reduction in joint tenderness, while group P (now taking zinc) improved in all of these parameters. These data are summarised in the table and changes in individual parameters are presented below.

Joint Swelling

The mean score in zinc-treated patients (group Z) fell from 27±3 (mean±S.E.M.) to 20±3 during the first 12 wk, while that of the placebo-treated individuals (group P) did not show a great change, 14±2 to 13±3. By the t test, the change in joint swelling was significant at each evaluation, with the mean difference over 12 wk being representative: $t=2.75$, $P<0.02$. Further declines in scores in both groups continued throughout the second, open period: Z, 20±3 to 17±4 and P, 13±3 to 9±2. Although comparison of the two groups is marred by the higher baseline in the zinc-treated group, the overall diminution of swelling with oral zinc was the clearest change observed.

Joint Tenderness

Improvement in joint tenderness was also observed, although the differences were not statistically significant during the double-blind period. The mean values at 0, 12, and 24 wk for group Z (28±5, 29±5, and 13±4) and for group P (28±5, 29±9, and 20±8) again showed improvement on oral zinc in group Z, while group P remained stable for 12 wk on placebo but then improved on oral zinc.

Morning Stiffness

During the double-blind trial, morning stiffness was significantly less in patients on zinc than in those on placebo at 4 and 8 wk. In the Z group, the mean morning-stiffness score fell from the initial value of 4·0±0·4 to 3·0±0·8 at 12 wk, with a further fall to 1·8±0·7 at 24 wk. Corresponding figures for the P group were 3·5±0·4, 3·6±0·5, and 2·7±0·5, again reflecting a stable course on placebo, with subsequent improvement while taking zinc sulphate.

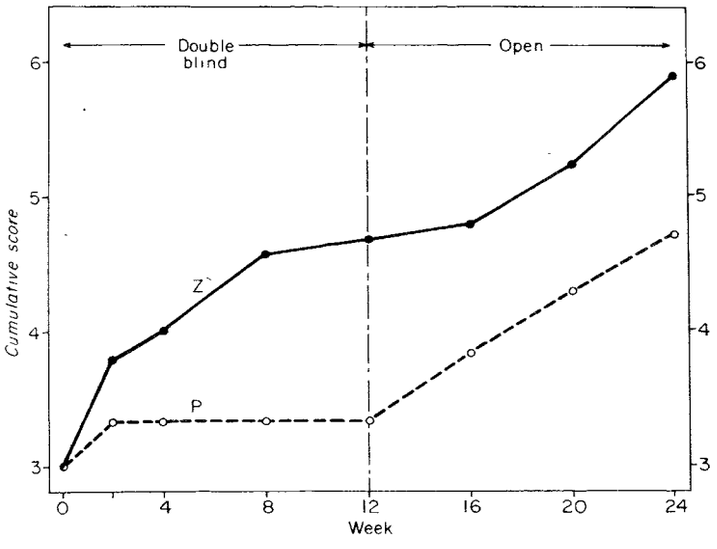
Grip Strength and Walking Time

Changes in grip strength were disappointing. An early improvement in the Z group was not sustained and P-group patients did not increase in strength during their 12 open weeks of zinc-sulphate therapy. In walking time, however, the mean time of the Z group improved

by three seconds during the double-blind trial and P-group patients then enjoyed some acceleration of walking time during their 12 wk on oral zinc.

Patient Assessments

In both "overall condition" and "change since last visit" there was a clear trend favouring zinc over placebo, with significant differences between the groups found at 4 and 8 wk for "overall" and "change" respectively. During the second 12 wk, both groups reported that their overall condition was good at each return visit on zinc therapy. In "change since last visit", each assessment relates only to its immediate predecessor. It is appropriate, however, also to consider this function in a cumulative way, as shown in the figure. Patients receiving zinc sulphate reported overall improvement at every evaluation interval during both the double-blind and the open phases of the trial. Patients receiving placebo, however, felt better at 2 wk but observed no further net change at 4, 8, and 12 wk. During the open phase of the trial these group-P patients reported progressive improvement at 16, 20, and 24 wk on zinc-sulphate therapy.



Cumulative plot of change since last visit.

Patients scored their overall progress "since last visit" on a scale of 5 (3 representing no change). The incremental change (average score minus 3) added to the previous score was plotted for each evaluation. Zinc-treated patients (z) felt better at every visit. Patients on placebo (P) scored higher at 2 wk, but did not improve further until they too took zinc sulphate in the open phase of the trial.

Hæmatology

There were no significant differences within or between the two groups in E.S.R., hæmatocrit, or W.B.C. count.

Serum Chemistry

Among the chemical determinations performed on serum at 0, 12, and 24 wk, significant changes were observed only in zinc, histidine, and alkaline phosphatase concentrations. Since there were no significant changes during the second 12 wk of continuous zinc treatment, the data are here combined for the first 12 wk of zinc treatment in all patients (0-12 wk in group Z and 12-24 wk in group P). The mean serum-zinc concentration rose only from 84±5 to 116±9 μg/dl after 12 wk of oral zinc. Although the increase is highly significant by paired t analysis ($t = 5{\cdot}06$, $P<0{\cdot}001$), the values both before and after therapy were well within the normal range (50–150 μg/dl). In individual patients, there was no apparent correlation between the degree of clinical improvement and the increase in serum-zinc concentration.

A slight fall in serum-histidine concentration was an unexpected finding. The mean histidine values before and after 12 wk of zinc therapy were 1·57±0·05 and 1·36±0·04 μg/dl, respectively. Although this difference was significant ($t = 3{\cdot}03$, $P<0{\cdot}005$), the individual changes in serum levels of zinc and histidine did not correlate with each other.

Serum-alkaline-phosphatase values rose from 79±24 to 96±27 U/l with oral zinc, and the increase in activity correlated highly with the rise in serum-zinc. These observations will be the subject of a separate report.

No significant changes were observed in the titre of rheumatoid factor or in the serum concentration of urate, sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, bilirubin, glucose, creatinine, or urea. Urinalyses did not change.

Serial radiographs of the hands revealed no significant changes in the bones although reduction of soft-tissue swelling was commonly seen.

Side-effects

Patients tolerated oral zinc sulphate well. In fact, the frequencies of headache, rash, change in appetite, abdominal pain or discomfort, and diarrhœa were all higher in the placebo group in the double-blind period. Nausea was reported three times in each group during the first period, but vomiting on one or more occasions was confined to three in the Z group. Constipation was more common in the Z group (5 patients) than in the P group (2). These possible side effects were all mild and none of them necessitated a change in treatment regimen. During the second 12-wk period, both groups tolerated zinc well.

Dropouts

Of the twenty-four patients enrolled, twenty-one completed all 24 wk of the trial. The three dropouts were from the Z group. One suffered from nausea when taking the capsules on an empty stomach, a second had a servere episode of diverticulitis, and the third had a flare-up of Still's disease, associated with a bleeding duodenal ulcer. Although each of these patients eventually resumed zinc sulphate without further complication, they did not complete the study, which left nine patients in the Z group throughout the trial and twelve in the P group.

Discussion

The results of this trial support the hypothesis that oral zinc sulphate might be beneficial to patients with rheumatoid arthritis. The significant improvements in joint swelling, morning stiffness, walking time, and the patients' assessment of overall condition suggest that articular function responded well to zinc during the dou-

ble-blind trial. The continuing improvement in these parameters over a subsequent 12-wk open period were also impressive to the examiners and to both groups of patients. It is unlikely that the stable refractory disease of these chronic patients improved solely by chance. Proof of this point, however, will require a larger, longer term, fully controlled study.

In addition to its apparent effectiveness, oral zinc sulphate was well tolerated. The emetic properties of this agent pose the only apparent problem in its use but can be circumvented by taking the medication with meals. Some foodstuffs interfere with zinc absorption, however, and it would therefore be desirable to establish and employ a zinc preparation which is more readily absorbed and can be taken by all subjects without gastrointestinal irritation. From our experience and that of others,[22 23] however, virtually all patients can tolerate oral zinc sulphate for 3 to 6 months. Possible toxic effects of prolonged use must still be carefully sought. In this context, the further decline of depressed serum-histidine levels must especially be watched.

This pilot study suggests that zinc supplementation may offer significant alleviation of many of the symptoms of active rheumatoid arthritis. Much additional work must be done, however, to confirm this observation, to determine the functions of zinc in both normal and diseased synovia, and to establish the appropriate place of oral zinc sulphate in the therapy of rheumatoid arthritis.

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CORRECTION OF ABNORMAL COAGULATION IN CHRONIC LIVER DISEASE BY COMBINED USE OF FRESH-FROZEN PLASMA AND PROTHROMBIN COMPLEX CONCENTRATES

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Summary The effect on abnormal coagulation tests of infusions of fresh-frozen plasma (F.F.P.), prothrombin complex concentrates, and a combination of these treatments was compared in 30 patients with chronic liver disease undergoing needle biopsy. A single dose of F.F.P. (12 ml/kg body-weight) was found to be the least effective therapeutic regimen. The concentrate containing factors II, IX, and X was also not adequate, but the additional administration of factor-VII concentrate corrected the prothrombin-time (P.T.) and 'Normotest' (N.T.) in most patients. However, this regimen did not correct the prolonged kaolin activated partial thromboplastin-time (K.P.T.T.). The results of tests for exploring both the extrinsic (P.T. and N.T.) and intrinsic (K.P.T.T.) coagulation systems only became normal after the combined administration of a lower dose of F.F.P. (8 ml/kg body-weight) and of both concentrates (12 units/ml). There was no clinical or laboratory evidence of thrombotic complications. No patient developed acute hepatitis or hepatitis-B surface antigen in the twelve months after biopsy. These results indicate that prothrombin-complex concentrates in combination with F.F.P. may therefore be used to allow liver biopsy to be performed safely in patients presenting with severe coagulation defects.

Introduction

CHRONIC liver disease is often associated with an acquired bleeding tendency. Although thrombocytopenia and hyperfibrinolysis may also be involved, defective synthesis by the hepatocyte of all the clotting proteins (except factor VIII) is thought to be an important causal factor.[1] Hence biopsy, laparoscopy, and other surgical procedures are accompanied by a risk of hæmorrhage unless the coagulation defect has been corrected. Fresh-frozen plasma (F.F.P.) which contains all the clotting factors, appears in principle to be the most useful therapeutic material. However, its use is limited by the large volumes which are usually needed; since these might aggravate the hypervolæmia often present in patients and lead to dangerous complications such as rupture of œsophageal varices or congestive heart-failure.

The availability of plasma derivatives containing in concentrated form clotting factors of the prothrombin complex (factors II, VII, IX, and X) has prompted us to compare the effects of concentrates and of F.F.P., alone or in combination, on coagulation tests in patients with chronic liver disease undergoing liver biopsy.

Material and Methods

Patients.—All patients requiring needle biopsy were screened for the presence of coagulation abnormalities by means of the following tests: prothrombin-time (P.T.) using