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Zinc in ulcerative colitis: a therapeutic trial and report on plasma levels

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SUMMARY A double-blind controlled trial of oral zinc sulphate as adjuvant treatment in idiopathic ulcerative colitis or proctitis in relapse is reported. Fifty-one patients were treated, and the clinical and sigmoidoscopic improvement in the zinc treated patients was similar to that in patients receiving placebo. No difference was found between plasma zinc levels in a further 46 patients with idiopathic ulcerative colitis or proctitis and those obtained in a group of healthy controls.

Oral zinc therapy has been shown to accelerate wound healing after pilonidal sinus excision (Pories *et al.*, 1967), to accelerate healing of varicose leg ulcers (Husain, 1969; Greaves and Skillen, 1970; Hallböök and Lanner, 1972) and sickle cell ulcers (Serjeant *et al.*, 1970), and to reverse the delayed healing caused by prolonged corticosteroid therapy (Flynn *et al.*, 1973). Solomons *et al.* (1974) found evidence of zinc deficiency in over half of the patients with inflammatory bowel disease whom they studied. We have therefore measured plasma zinc levels in a number of patients with idiopathic ulcerative colitis and proctitis, and have assessed in a double blind trial the benefit of oral zinc sulphate as an adjuvant to treatment of established efficacy in ulcerative colitis in relapse.

Methods

1. THERAPEUTIC TRIAL

Patient selection and treatment

Outpatients with first attacks or relapses of idiopathic left-sided ulcerative colitis or proctitis were entered into the trial and all with radiological disease proximal to the splenic flexure were excluded. All had symptoms referable to their bowel disease at the onset of the study and all had abnormal sigmoidoscopic appearances.

Patients were allocated by a prearranged randomised schedule to either zinc sulphate capsules 220 mg three times daily, or an apparently identical placebo (glucose) capsule for four weeks, neither doctor nor patient knowing which treatment was given. In addition, patients were treated as indicated clinically with sulphasalazine 1 g three times daily, or prednisolone 10 mg three times daily, or 20 mg prednisolone retention enemata each night.

Patients were seen at the start of treatment and after two and four weeks. At each visit bowel frequency and consistency were recorded along with the presence or absence of blood and mucus. In addition blood haemoglobin and erythrocyte sedimentation rate (ESR) were measured on each visit, and sigmoidoscopy was performed. Sigmoidoscopic appearances were graded thus: 4—severely haemorrhagic mucosa with bleeding seen ahead of the instrument; 3—moderately haemorrhagic with bleeding to light touch; 2—not haemorrhagic but abnormal with granularity and loss of vascular pattern; 1—normal.

Persisting abdominal pain, diarrhoea, or constipation were treated at the second visit with propantheline, codeine phosphate, or magnesium sulphate. Treatment was continued for four weeks unless remission had occurred by two weeks. No inquiries were made about side-effects but they were recorded if complained of spontaneously.

2. PLASMA ZINC LEVELS

Plasma zinc levels were measured in 46 patients with idiopathic ulcerative colitis or proctitis (24 male, 22 female, mean age 42 years), and in 34 controls. Twenty-two of the patients had relapse of their disease at the time of venesection as judged symptomatically and sigmoidoscopically, while 24 were in remission. The disease was confined to the rectum in 14 patients, while in 22 patients disease was

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present radiologically distal to the splenic flexure, the remaining 10 patients having disease proximal to the splenic flexure. Thirteen patients were on no therapy at the time of venesection, while 25 were receiving sulphasalazine and 13 corticosteroid therapy, some patients receiving multiple therapy. The controls were healthy nursing, medical, and laboratory staff aged between 20 and 50 years.

Ten millilitres of venous blood were collected into a tube containing lithium heparin. Plasma was separated by centrifugation, and stored at −20°C until zinc measurement was performed. For analysis, one part plasma was diluted with nine parts deionised water and zinc levels measured by flame atomic absorption spectrometry (Instrumentation Laboratories 251) (Hackley *et al.*, 1968).

Results

1. THERAPEUTIC TRIAL

Comparability of patients

Fifty-one patients entered the trial, 26 receiving the zinc capsules and 25 the placebo. Those in the zinc and placebo groups were similar in age and sex distributions, in length of attack, total disease duration and radiological extent of disease, and in initial haemoglobin and ESR (Table 1). There was no difference in the two groups in bowel consistency and frequency of blood and mucus in the motions. The numbers of patients prescribed sulphasalazine, rectal prednisolone, and oral prednisolone were also similar in each group.

Clinical results

Improvement of symptoms of bowel consistency and frequency, and in the passage of blood and mucus were assessed on a points system. A change in bowel consistency from loose to formed was awarded 2 points; from loose to semi-formed 1 point; and from semi-formed to formed 1 point. An improvement in bowel frequency from six or more a day to two or less a day was given 2 points; from six or more a day to between three and five a day 1 point; and from between three and five a day to two or less a day 1 point. Complete disappearance of blood and mucus from the stool was awarded 2 points each, while a lessening of the amount passed received 1 point. Thus the maximum possible point score for symptomatic improvement in any patient with severe initial symptoms would be 8.

Table 2 shows that improvement tended to be slightly greater in those receiving zinc than in those given the placebo, 12 out of the 26 (46·2%) of those receiving zinc capsules improving by 6 points or more compared with eight of the 25 (32%) given the placebo, but this difference could well have been due to chance ($P = 0{\cdot}37$, Mann-Whitney U test). Sigmoidoscopic improvement was also assessed on a points system. A change in appearance from grade 4 to grade 1 or 2 was awarded 2 points. One point was awarded to a change from grade 4 to grade 3, grade 3 to 1 or 2, and grade 2 to 1. The points thus scored for the two groups of patients are shown in Table 3, and clearly there is no significant difference between the two groups.

No change occurred in haemoglobin levels during treatment but there was a slightly greater fall in mean ESR in those receiving the placebo than in those receiving zinc (means 10·7 and 6·9 respectively).

No side-effects were recorded other than those attributable to systemic steroid therapy.

Table 1 *Comparability of patients in therapeutic trial*

	Zinc treatment	*Placebo treatment*
Men	13	13
Women	13	12
Median disease duration (months)	24	24
Median attack duration (months)	2	2
Barium enema: normal	12	11
Rectosigmoid disease	9	8
Diffuse left-sided disease	5	6
Initial mean bowel frequency/day	5·4	3·9
Initial mean haemoglobin (g/dl)	13·2	13·0
Initial mean ESR (mm/h)	18	18
Other treatment prescribed:		
Sulphasalazine	3	4
Oral prednisolone	10	12
Rectal prednisolone	13	9

Table 2 *Clinical improvement during therapeutic trial*

*Points**	*Zinc*	*Placebo*
8	XXX	XX
7	XXXX	XXX
6	XXXXX	XXX
5	XXX	XXXXX
4	XXX	XXXX
3	XXXX	XX
2	XXX	XX
1		XX
0	X	XX
Mean points score (± standard deviation)	4·9 ± 2·2	4·3 ± 2·4

*For point scoring system see text.

Table 3 *Sigmoidoscopic improvement during therapeutic trial*

*Points**	*Zinc*	*Placebo*
2	13	12
1	9	8
0	4	5

*For point scoring system see text.

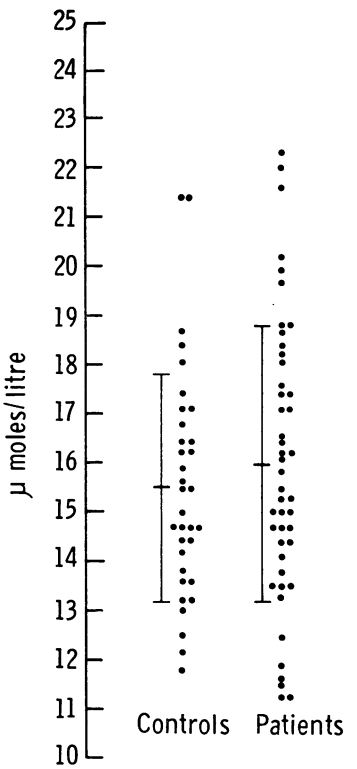

Figure *Plasma zinc levels in patients and controls. Mean levels (horizontal bar) and standard deviation are shown.*

2. PLASMA ZINC LEVELS

The distribution of plasma zinc levels in the patients (mean 16·0 ± standard deviation 2·8 μmol/l) was indistinguishable from that in the controls (15·5 ± 2·30 μmol/l), as shown in the Figure. No correlation was found in the patients between plasma zinc levels and disease activity, extent, duration, or therapy.

Discussion

We have been unable to demonstrate low plasma zinc levels in a group of patients with ulcerative colitis of all grades of severity. Normal plasma levels do not, however, exclude zinc deficiency, which can probably only be firmly assessed by total body counting techniques (*Lancet*, 1975).

The role of zinc in gastrointestinal disease has received little attention. While there is no doubt about the presence of zinc deficiency in acrodermatitis enteropathica and of the dramatic response of the diarrhoea in this condition to oral zinc therapy (Moynahan, 1974), the role of zinc in other gastrointestinal disease is less clear.

Low plasma zinc levels have been found in alcoholic and other liver disease (Halsted and Smith, 1974) and in patients with inflammatory bowel disease (Solomons *et al.*, 1973), though only nine patients in the latter study had ulcerative colitis. Plasma levels have been found to be normal in gastric ulcer (Frommer, 1975), but in two therapeutic trials oral zinc treatment appeared to accelerate ulcer healing (Fraser *et al.*, 1972; Frommer, 1975).

The results of our study show that oral zinc sulphate is of no benefit as an adjuvant to already established treatment in the management of relapse of ulcerative colitis. We did not think it was ethical to treat patients in relapse with zinc or placebo alone, withholding proven effective therapy (Truelove and Witts, 1955; Baron *et al.*, 1962). It is therefore still possible that zinc has a beneficial effect which was obscured by the other treatments prescribed.

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References

Baron, J. H., Connell, A. M., Lennard-Jones, J. E., and Avery Jones, F. (1962). Sulphasalazine and salicylazosulphadimidine in ulcerative colitis. *Lancet*, **1**, 1094-1096.

Flynn, A., Strain, W. H., Pories, W. J., and Hill, O. A. Jr. (1973). Zinc deficiency with altered adrenocortical function and its relation to delayed healing. *Lancet*, **1**, 789-791.

Fraser, P. M., Doll, R., Langman, M. J. S., Misiewicz, J. J., and Shawdon, H. H. (1972). Clinical trial of a new carbenoxolone analogue (BX 24), zinc sulphate, and vitamin A in the treatment of gastric ulcer. *Gut*, **13**, 459-463.

Frommer, D. J. (1975). The healing of gastric ulcers by zinc sulphate. *Medical Journal of Australia*, **2**, 793-796.

Greaves, M. W., and Skillen, A. W. (1970). Effects of long-continued ingestion of zinc sulphate in patients with venous leg ulceration. *Lancet*, **2**, 889-891.

Hackley, B. M., Smith, J. C., and Halsted, J. A. (1968). A simplified method for plasma zinc determination by atomic absorption spectrophotometry. *Clinical Chemistry*, **14**, 1-5.

Hallböök, T., and Lanner, E. (1972). Serum-zinc and healing of venous leg ulcers. *Lancet*, **2**, 780-782.

Halsted, J. A., and Smith, J. C., Jr. (1970). Plasma-zinc in health and disease. *Lancet*, **1**, 322-324.

Husain, S. L. (1969). Oral zinc sulphate in leg ulcers. *Lancet*, **1**, 1069-1071.

Lancet (1975). Leading article. Zinc in human medicine. *Lancet*, **2**, 351-352.

Moynahan, E. J (1974). Acrodermatitis enteropathica: a lethal inherited human zinc-deficiency disorder (Letter). *Lancet*, **2**, 399-400.

Pories, W. J., Henzel, J. H., Rob, C. G., and Strain, W. H. (1967). Acceleration of wound healing in man with zinc sulphate given by mouth. *Lancet*, **1**, 121-124.

Serjeant, G. R., Galloway, R. E., and Gueri, M. C. (1970). Oral zinc sulphate in sickle-cell ulcers. *Lancet*, **2**, 891-892.

Solomons, N. W., Vo-Khactu, K., Sandstead, H. H., and

Rosenberg, I. H. (1974). Zinc nutrition in inflammatory bowel disease. In *Fifth World Congress of Gastroenterology*, Abstract, p. 263. Mexican Society of Gastroenterology: Mexico City.

Truelove, S. C., and Witts, L. J. (1955). Cortisone in ulcerative colitis: final report on a therapeutic trial. *British Medical Journal*, **2**, 1041-1048.

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