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Serum zinc, bronchiectasis, and bronchial carcinoma

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Beeley, J. M., Darke, C. S., Owen, G., and Cooper, R. D. (1974). *Thorax*, **29**, 21–25. **Serum zinc, bronchiectasis, and bronchial carcinoma.** Serum zinc levels were measured by atomic absorption spectrophotometry in 65 patients with proven bronchiectasis; the mean level was 93 μg/100 ml, while the levels in two groups of healthy control subjects were 88·6 and 92·7 μg/100 ml respectively. The range of individual values was similar in all groups and the differences between the mean serum zinc levels of the two groups of control subjects and the mean level of the group of patients with bronchiectasis were small and did not attain significance at the conventional 0·05 level. In contrast, the mean level in bronchial carcinoma patients (75·9 μg/100 ml) was significantly less than in each of the other groups of subjects.

Zinc sulphate was administered for six weeks on a double-blind cross-over basis to patients with bronchiectasis and, although serum zinc levels rose, no detectable clinical improvement resulted. No definitive evidence of zinc deficiency in bronchiectasis has been established.

There is now substantial evidence that oral zinc sulphate therapy promotes the healing of excised wounds (Pories, Henzel, Rob, and Strain, 1967), venous leg ulcers (Husain, 1969; Greaves and Skillen, 1970; Hallböök and Lanner, 1972), and sickle-cell ulcers (Serjeant, Galloway, and Gueri, 1970). The rationale for the use of zinc to promote tissue repair is based on the demonstration of preferential concentration of zinc at wound margins in human subjects (Savlov, Strain, and Huegin, 1962) and mobilization of zinc-65 to the site of bone fracture in rats (Calhoun and Smith, 1968).

Reduced levels of both plasma and serum zinc have been reported in patients with chronic pulmonary infection (Halstead and Smith, 1970; Sinha and Gabrieli, 1970). Administration of zinc sulphate has been reported to accelerate the healing of post-intubation tracheal granulomata (Pullen, 1970) and to produce a striking reduction of purulent exudate in venous leg ulcers (Husain, 1969). In bronchiectasis the smaller airways show mucosal ulcers lined with granulation tissue from which pus streams into the bronchial lumen (Whitwell, 1952), leading to expectoration of purulent sputum. Improvement results when these ulcers become covered by cells advancing from the adjoining epithelium.

The purpose of this trial was to determine the serum zinc levels in a series of patients suffering from bronchiectasis and to determine whether oral zinc sulphate administration raised the serum level and produced clinical improvement.

PATIENTS AND METHODS

SERUM ZINC MEASUREMENTS Measurements of zinc content were made on sera from the following: (1) control subjects who were either healthy members of the hospital staff or blood donors; (2) patients with proven bronchiectasis, including those to whom zinc sulphate would be administered in the trial; (3) patients with bronchial carcinoma. The latter group were studied as low levels of plasma zinc have been reported in this disorder (Davies, Musa, and Dormandy, 1968) and we wished to determine whether low levels occurred also in the serum.

Serum zinc levels were measured using an EEL 140 atomic absorption spectrophotometer. Reproducibility of the method was tested using AA reference standards obtained from the Fisher Corporation. Nine measurements were carried out on each of 12 unknown test sera and produced a standard deviation of 3 μg/100 ml. Venous blood samples were withdrawn by zinc-free plastic syringes and placed in zinc-free centrifuge tubes. After clotting, the blood was centrifuged at 3,500 rev/min for five minutes and the resulting serum was transferred to plastic containers and stored at 4°C until the estimation. Serum specimens in which haemolysis had occurred were discarded. Before estimation, equal volumes of zinc-free 10% trichloracetic acid were added to the sera, and the zinc content of the protein-free supernatant was then determined. We found that the addition of EDTA to

blood before separation of serum did not produce significantly different zinc levels in a series of paired specimens, and it was therefore not used during preparation of the specimens.

ZINC SULPHATE ADMINISTRATION Thirty-three patients with bronchographically proven bronchiectasis agreed to take oral zinc sulphate for six weeks after the experimental nature of the trial had been explained to them. It was required that they should have a normal blood urea and that their sputum be constantly purulent except during antibiotic administration so that any change in sputum character could easily be detected. Each patient was supplied with capsules containing 220 mg of zinc sulphate or an identical placebo to take three times daily after meals for six weeks and then crossed over to the alternative therapy for a similar period. The capsules were dispensed by the hospital pharmacist according to a previously arranged random allocation procedure. After an initial visit, patients were seen at two-week intervals throughout the trial period when the following assessments were made:

Sputum volume Each patient collected all sputum for 24 hours before attendance and, separately, that expectorated on rising on the morning of attendance for volume assessment.

Sputum purulence Both 24-hour and morning sputum specimens were assessed for purulence by two observers, one of whom was present at all attendances. The specimens were graded according to an established technique (Miller and Jones, 1963) into one of five recommended categories (M1=pure mucoid; M2=suspicion of pus; P1=less than $\frac{1}{3}$ pus; P2=$\frac{1}{3}$–$\frac{2}{3}$ pus; P3=more than $\frac{2}{3}$ pus).

Bacteriology The fresh specimen of sputum collected on the morning of attendance was sent to the Bacteriology Department and an inoculation was made from the most purulent part of the specimen onto blood agar, chocolate agar, and McConkey media, incubated for 18 to 24 hours at 37°C, and then examined for recognized pathogens.

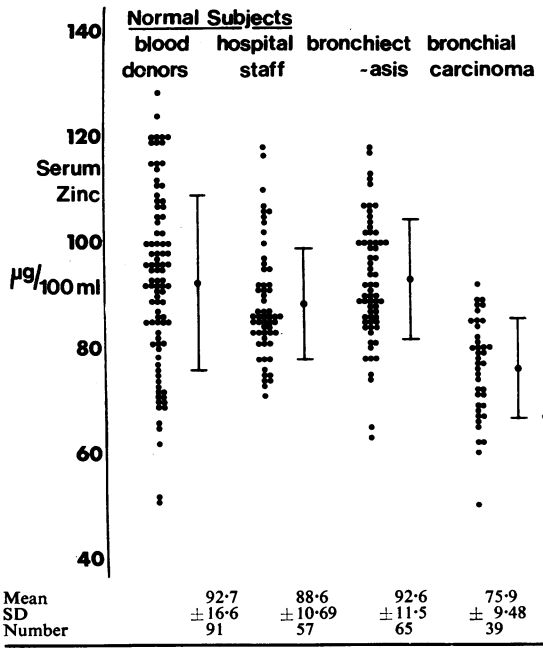
Other parameters At each attendance intercurrent antibiotic therapy, exacerbation of cough or sputum, and any side effects were noted; the best of three blows into a Wright peak flow meter and a measurement of serum zinc, to which the observers were kept blind, were made. The following biochemical tests were performed on each patient at the end of each six-week period: serum aspartate aminotransferase, serum alanine aminotransferase, serum proteins, and electrophoretic strip.

RESULTS

SERUM ZINC LEVELS IN CONTROLS, BRONCHIECTASIS, AND BRONCHIAL CARCINOMA The distribution of serum zinc levels in two separate groups of healthy control subjects, in patients with bronchiectasis, and in others with bronchial carcinoma is shown in Table I. It can be seen that the mean zinc level in bronchiectasis was similar to that in the control subjects. The mean serum zinc level in patients with bronchial carcinoma was, however, significantly lower than in the blood donors (t=5·94; P<0·001) or the hospital staff controls (t=5·97; P<0·001).

TABLE I

SERUM ZINC VALUES IN CONTROL SUBJECTS, BRONCHIECTASIS, AND BRONCHIAL CARCINOMA



During the course of the trial 14 patients were shown retrospectively to have received placebo first. In these patients, therefore, serum zinc estimations were available from four attendances before zinc therapy was started. These specimens were taken at two-week intervals and have shown an 'in-patient variance' of 195·7. This represents a standard deviation for repeat estimations on the same patient of 14·0.

RESULTS OF ZINC ADMINISTRATION (27 patients) Twenty-seven patients, of whom 15 were females, completed the trial and were admitted for assessment; six were eliminated from analysis, having failed either to take treatment or to attend as directed.

SERUM ZINC LEVELS Mean serum zinc levels rose during oral zinc therapy, indicating that zinc had been taken by the patients and had resulted in a

statistically significant rise in serum zinc (see Table II).

TABLE II

MEAN SERUM ZINC LEVELS DURING THE TRIAL (27 PATIENTS)

	Pre-treatment (1 visit)	Placebo (3 visits)	Zinc (3 visits)	Significance *t* Test		
				Pre *v* Plac	Pre *v* Zinc	Plac *v* Zinc
Mean serum zinc (μg/100 ml)	98·5	88·5	122·9	3·95	−4·56	−6·55
SD	±9·3	±10·8	±33·1	P < 0·001	P < 0·001	P < 0·001

SPUTUM VOLUME The mean 24-hour volume of sputum expectorated by patients during the periods on placebo and zinc were similar (Table III). There was a fall in sputum volumes from that obtained on the initial pre-treatment visit, which is probably explained by their entry into the trial during a sputum-productive period and by a more complete collection at the initial visit; this behaviour was seen irrespective of the order in which the two drugs were given. Thereafter sputum collections did not fall off significantly. Morning sputum volumes were not significantly altered during the trial.

SPUTUM PURULENCE In Table III sputum graded M1 or M2 is recorded as 'mucoid' and if P1 to P3 as 'purulent'. Grading of purulence of 24-hour sputum specimens was similar during placebo and zinc administration. There were, however, reductions in the proportion of purulent specimens when compared with the pre-treatment specimens, which is explained by the criteria of purulence for entry into the trial. Similar trends were seen in the assessment of morning specimens.

Sputum bacteriology Morning sputum cultures showed a similar number of organisms isolated during the periods on zinc and placebo (Table IV). Approximately one-third of the 189 sputum specimens cultured yielded bacteria. *Haemophilus influenzae* was the bacterium in 50% of instances, *Streptococcus pneumoniae* in 25%, coliform bacilli in 13%, and *Proteus mirabilis, Pseudomonas aeruginosa, Entamoeba coli* or *Staphylococcus aureus* in the remainder. These pathogens were evenly distributed throughout the patients receiving zinc and placebo. In six of the 27 patients pathogens were not cultured at any of the seven visits.

Other parameters (Table IV) More patients received antibiotics during the period of zinc therapy than during placebo administration. Exacerbations were similar in incidence during each of the trial periods. There was no significant change in peak flow readings, though a small improvement occurred from the pre-treatment measurement, which is likely to be due to a learning effect.

Side effects Three patients suffered transient cramp-like epigastric pain after taking zinc sulphate before meals but they had no further trouble when they subsequently took treatment after meals as originally directed. No other adverse symptoms were reported. Transaminases, serum proteins, and electrophoretic strip remained undisturbed in all patients throughout the trial.

TABLE III

EFFECTS OF ZINC SULPHATE ADMINISTRATION ON SPUTUM VOLUME AND PURULENCE

Measurement	Pre-treatment (1 visit)	Placebo (3 visits)	Zinc (3 visits)	Significance *t* Test		
				Pre *v* Plac	Pre *v* Zinc	Plac *v* Zinc
24-hour sputum vol. (ml)						
Mean	36·2	28·0	27·3	2·18	3·50	0·29
SD	22·3	18·6	19·7	P < 0·05	P < 0·01	ns
Morning sputum vol. (ml)						
Mean	3·8	3·6	4·1	0·57	−0·46	−1·18
SD	2·7	2·7	4·1	ns	ns	ns
No. of 24-hour sputum specimens						
Purulent	27 (100%)	66 (81%)	74 (91%)			
Mucoid	0	15	7			
No. of morning sputum specimens						
Purulent	25 (93%)	61 (75%)	59 (73%)			
Mucoid	2	20	22			

TABLE IV

EFFECTS OF ZINC SULPHATE ADMINISTRATION ON MAXIMUM PEAK FLOW RATE, EXACERBATIONS OF COUGH, SPUTUM CULTURE, AND ANTIBIOTIC REQUIREMENTS

Measurement	Pre-treatment (1 visit)	Placebo (3 visits)	Zinc (3 visits)	Significance *t* Test		
				Pre *v* Plac	Pre *v* Zinc	Plac *v* Zinc
Peak flow rate (l/min)						
Mean	253·0	264·3	264·4	−1·83	1·73	−0·03
SD	116·6	115·7	118·2	ns	ns	ns
Exacerbations of cough						
Yes	4 (15%)	10 (37%)	13 (48%)			
No	23	17	14			
Sputum culture (no. of specimens)						
Positive	11 (65%)	28 (35%)	30 (37%)			
Negative	6	53	51			
Antibiotic administration						
Yes	4 (15%)	8 (30%)	15 (55%)			
No	23	19	12			

DISCUSSION

Evidence that zinc may be of therapeutic value in the treatment of cutaneous ulcers has encouraged workers to administer oral zinc sulphate to a wider range of disorders, including gastric ulcer (Fraser *et al.*, 1972). Reduced plasma zinc levels have been reported in pulmonary infection but were based on values obtained in only eight patients (Halstead and Smith, 1970). Some support, however, was given to the possibility that pulmonary infection might be associated with a low level of zinc in the blood by workers who measured serum levels in 40 patients with bronchitis (Sinha and Gabrieli, 1970). Low serum or plasma zinc levels in infection could be of significance in view of the role of zinc in tissue repair, and particularly as it has been stated that zinc has an effect on bacteria (Goodman and Gilman, 1970).

Mean serum zinc levels and the range of individual values in our study of 65 patients with bronchiectasis have been shown to be of the same order as those of two separate groups of normal control subjects. In addition, the administration of oral zinc sulphate under controlled conditions to 27 patients has failed to produce any detectable improvement. Our investigations have, therefore, produced no evidence of zinc deficiency or any indication that oral zinc administration has a useful role in bronchiectasis. At the same time low mean zinc levels have been demonstrated in the serum of patients with bronchial carcinoma, which supports an earlier study (Davies, Musa, and Dormandy, 1968) in which plasma levels were measured. The significance of this latter finding is not yet established, though it has been shown that zinc can protect hamsters against experimentally induced carcinoma (Poswillo and Cohen, 1971).

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