

ORAL ZINC IN ACNE

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In Sweden, and also in Denmark and Norway, zinc has been tried for some time in the treatment of acne. I would like to summarize and discuss the results obtained by us and others.

The striking effect of zinc on severe pustular acne in a patient with acrodermatitis enteropathica aroused our interest in zinc and acne (Fig. 1, 2). The effect of zinc on acne in patients with this disease has later been confirmed by others. But, does this mean that oral zinc also has an effect on acne in otherwise healthy patients without any obvious clinical signs of zinc deficiency? The answer to this question has varied. We found a good effect, some others a moderate effect and others no effect at all. What is true? How can the

discrepancies be explained? To a certain extent these discrepancies may be explained by differences in response to zinc by various types of acne.

In our first study we obtained good results with zinc (1). This study included 64 patients with mainly grade III and IV acne; many of them had a long history of severe acne in spite of their relatively low mean age. Two-thirds of the patients were between 14 and 18 years of age. Twenty percent previously had failed to respond to tetracyclines. We started with four treatment groups:

- a) Solvezink® (Zn⁺⁺ 45 mg) 1 tablet three times daily.
- b) Placebo zinc 1 tablet three times daily.
- c) Arovit® drops (Vitamin A 150.000 IU/ml) 25 drops twice daily.
- d) Solvezink®, 1 tablet three times daily and Arovit® drops, 25 drops twice daily.



Fig. 1. Before zinc treatment.

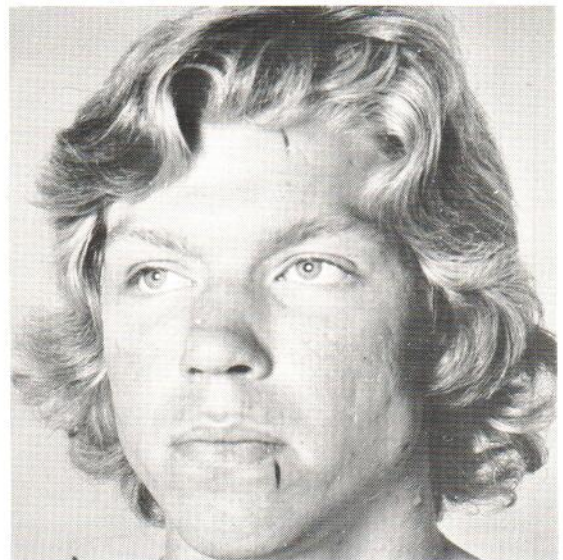


Fig. 2. After zinc treatment.

During the first four weeks group (a) and (b) were treated and evaluated in a double-blind fashion. The results were evaluated by counting the various types of lesions, by making an acne "score", by photographic records, and by the general opinion of the patients and doctor of the degree of improvement. The best response was seen with pustules and infiltrated lesions, whereas we could see no influence on the comedones. All patients completed the study. The overall results are illustrated in Fig. 3 which is based upon the percentage decrease of the mean score of the four treatment groups. There was considerable improvement within four weeks in the zinc-treated groups, whereas the effects seen in the placebo- and vitamin A-treated groups were not as great. When zinc was given to these groups, the same improvement occurred as in the groups first given zinc.

The next study was published by Weismann et al (2) and compared the effect of zinc with that of a placebo. They used the same dosage of zinc but found no differences in effect between zinc and the placebo. The effects were quite good both in the placebo- and zinc-treated patients. This study was done from

March through June and the weather was sunny during the study. Their patients had a higher mean age (22 years for the men and 24 for the women) and they did not include any patients previously treated with tetracyclines, topical vitamin-A-acid or benzoyl peroxide. This might possibly indicate that they had patients with milder acne than those included in our study. Unfortunately, they also had a 30 percent drop-out of the patients. In their study one puzzling thing was that the serum zinc levels increased not only in the zinc-treated group but also in the placebo-treated group.

Another comparison of zinc and a placebo has been done by Hillström et al in Sweden (3) including 91 patients with grade II—III acne. This was a multicenter, double-blind study that was done from November to March in a group of patients with a mean age of 18 years. Lower doses of zinc were used than in our study. They found a significantly better effect of zinc than of the placebo.

A double-blind study of zinc and a placebo has also been done by Göransson et al (4). They had 54 patients with grade I—III acne. The effect of zinc was significantly better than that of the placebo but not as good as reported by us. Three possibly important differences in their study as compared with our first study are that their study was undertaken during a period with minimal daylight, that it lasted for only six weeks, and that they included not only grade II and III acne but also grade I acne.

A double-blind comparison between zinc and oxy-tetracycline has been done by our group in Uppsala

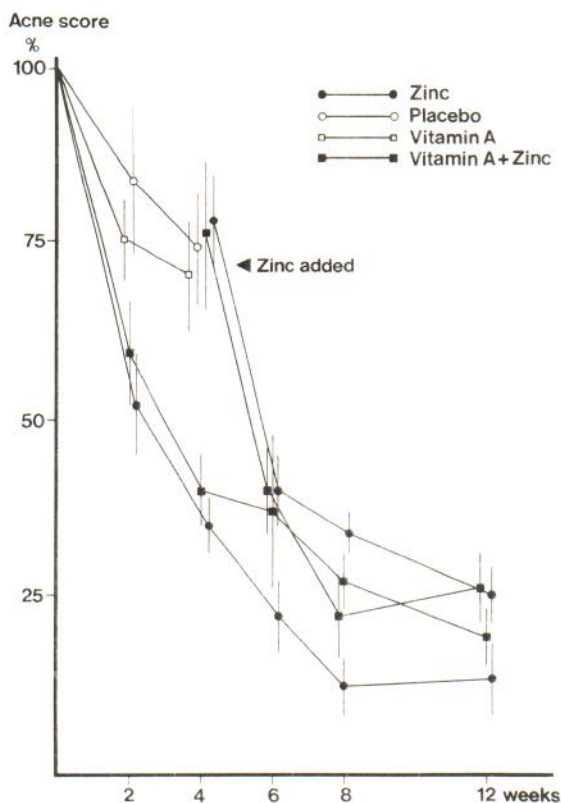


Fig. 3. Overall treatment results expressed as "Score" (1).

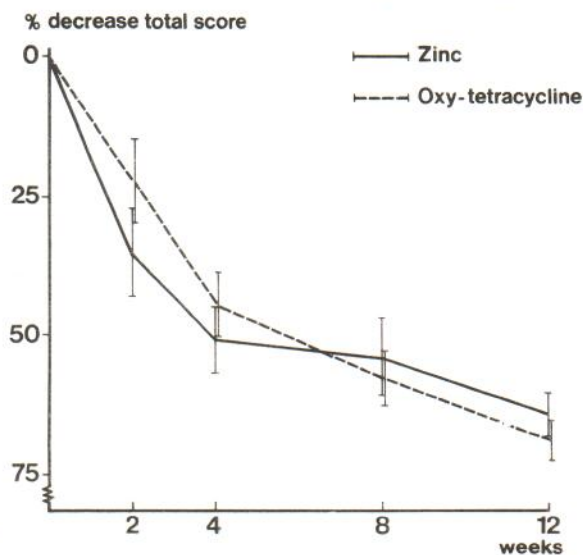


Fig. 4. Overall treatment results expressed as "Score" (5).

with a double-dummy technique (5). Most patients were treated between November and March. The 40 patients, whose mean age was about 18, had mainly grade III and IV acne, although there were also some patients with grade II acne. The dosage of the oxytetracycline (Oxy-Dumocyclin®) was 250 mg three times daily between meals during the first two weeks, 250 mg twice daily during weeks 3 and 4, and 250 mg once daily weeks 5 to 12. Zinc (Solvezink®) was given 1 tablet three times daily throughout the study. The results were evaluated by several methods. No difference in effect between the treatments was seen with any of the evaluation methods. The percentage decrease of the total score is shown in Fig. 4 and is about 65 percent for both groups. Similar results have been found by Haavelsrud in Norway (6).

The answer to the question, "Does oral zinc have an effect on acne?" is, in my opinion, based on the results of the studies referred to today as well as on personal experience, that zinc has an effect in many patients with inflammatory acne. There are no studies on the effects in mild acne, but the lack of effect on comedones makes it likely that zinc has little effect on

a very mild acne. We now often use zinc as the first drug in patients with pronounced acne where we believe that topical treatment is insufficient. In boys with the most severe types of acne, we sometimes double the dose of zinc for the first few weeks.

Examples of the effect of zinc in three patients with three different types of acne are shown in Figs. 5—10. The girl in Fig. 5 and 6 had superficial papules and pustules and was nearly healed after zinc taken for 12 weeks. The girl in Fig. 7 and 8 had a seven-year-long history of very severe acne and had been treated with absolutely everything without any improvement. She had numerous infiltrated lesions and cysts. After a few weeks of zinc therapy, she was much improved and after 4 months nearly healed (Fig. 8). A third patient, a boy; 15 years of age (Fig. 9), had moderate acne since the age of 12. He had a severe flare of his acne during three months associated with a weight loss of 7 kilos, fatigue, fever of 38°C, joint pains, anemia, and an ESR of 94 mm. High doses of tetracyclines were given without effect. He was then treated with 3—6 Solvezink tablets a day. After seven days, a subjective improvement of all symptoms was seen and,

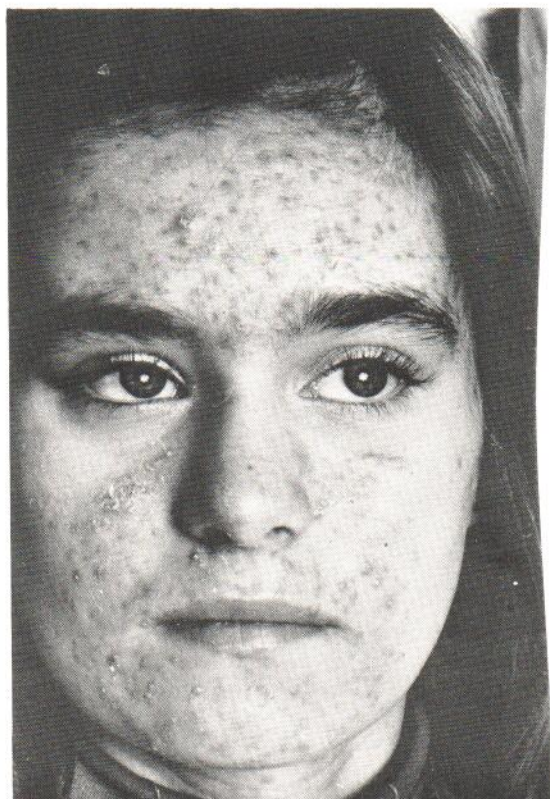


Fig. 5. Before zinc treatment.

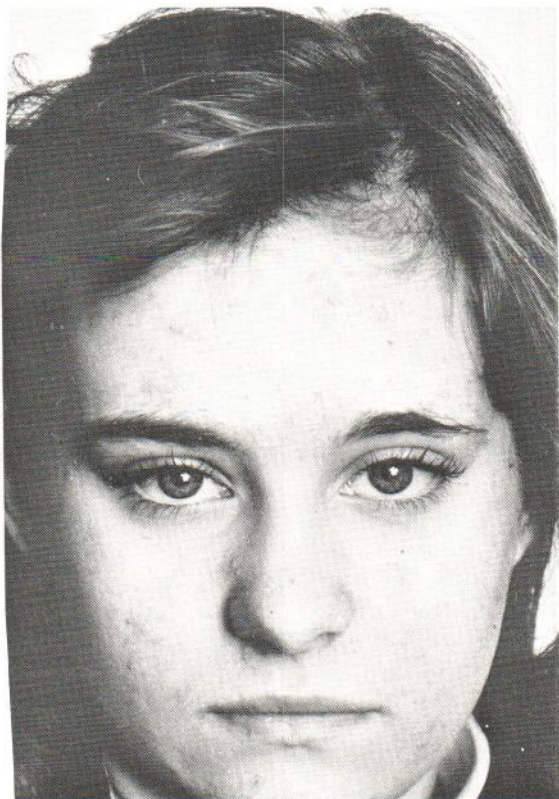


Fig. 6. After zinc treatment.



Fig. 7. Before zinc treatment.



Fig. 8. After zinc treatment.



Fig. 9. Before zinc treatment.

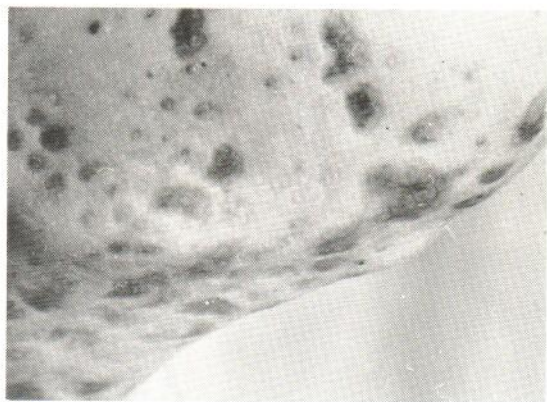


Fig. 10. After zinc treatment.

after two weeks he noted a definite improvement of his acne. After eight weeks, he had no joint pains, his weight had increased 6 kilos, there was a reduction of the ESR from 94 to 20 mm, and there was further improvement of his acne (Fig. 10). Several boys with acne of this type have been treated with oral zinc with the same good result both in respect to their acne and their general symptoms.

There have been few side-effects from zinc treatment in our patients with acne, although zinc salts are known to often produce gastric irritation. With the special preparation we use, these effects are much less frequent than if zinc sulphate capsules or tablets are used. We have very rarely heard of any complaints in this age group. We always tell our patients that they might have some gastric symptoms and that it is important to take zinc after meals. In a retrospective study of 104 patients (66 boys and 38 girls), only one girl had to discontinue treatment because of gastric ir-

ritation. Another of the girls experienced gastric irritation with 3 tablets a day but tolerated 2 tablets a day, and a third developed gastric irritation after one year's treatment. There was no influence on the haemoglobin, WBC or transaminases. We have seen no cases with low serum copper levels during treatment with zinc.

The mechanism of the effect of zinc in acne is not quite clear. There is very little knowledge of the status of the sebaceous glands in zinc-deficient animals and no studies in humans. In 1941 Follis et al (7), in their study on the effect of zinc deficiency in rats, found epithelial hypertrophy, keratinization of the hair follicles, and hypertrophy of the sebaceous glands. Recently, Baer & King (8) described experimental effects of zinc deficiency in young healthy men. They studied the effect of a low zinc diet in six young, healthy male volunteers. Within three weeks of depletion, one of these six subjects developed severe acne, which

promptly improved with zinc repletion. Others displayed more pustules than usual, whereas others had a drier skin. Their results suggest that the response to low dietary zinc varies greatly among individuals. With regard to their findings, as well as to the effects of zinc on acne in acrodermatitis patients, it seems reasonable to assume that zinc deficiency worsens or provokes acne and also that, if there is a zinc deficiency in acne patients, oral zinc would be beneficial. The fact that we found that healthy boys 13 to 15 years of age have a somewhat lower serum zinc than boys of other ages and also that boys with grade III and IV acne have lower zinc levels than those with mild acne (10) is noteworthy. It is known that especially boys need extra zinc during their pubertal development. In some cases it is possible that zinc acts by correcting a zinc deficiency. Zinc may, however, also act as an anti-inflammatory agent. This has been suggested by Chvapil et al (11). This may then explain the effect on the inflammatory lesions. Our idea that zinc may influence the low serum vitamin A in acne has not been verified; at least the serum levels of vitamin A remain unchanged during zinc therapy (12).

To summarize: our present opinion is that oral zinc has a positive effect on grade III and IV acne. The mechanism of action is not clear. Zinc may act as an anti-inflammatory agent but it has also been shown that zinc deficiency induces or worsens acne. We have seen few side-effects of oral zinc in acne. I think that the time may come when we have to discuss whether supplements with oral zinc, especially for acne-prone boys, should be given during puberty development.

DISCUSSION

Cunliffe, Leeds: Three points, if I may? Firstly, we had the opportunity to study quite a lot of patients deficient in zinc. They got acne-like lesions, but to me it is not what we call acne in the clinical sense. My other point is that there is evidence that zinc is anti-chemotactic and that may explain its role in the severe cases of acne. The third point is that Mr. Odsell and Dr. Juhlin have kindly asked me to comment on a trial we have been doing in Leeds in the last three months with Draco. Briefly, we looked at 50 patients. We had eight drop-outs, four in each group. In the tetracycline group, which we were comparing with the zinc, three of the patients we lost for no reason;

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one became pregnant, I do not know what happened to her! In the zinc group we had two patients who developed a deterioration in their acne and wished to withdraw from the trial and two who developed quite marked gastrointestinal symptoms and again had to stop. When we came to analyze the patients, we had equal numbers at the end of the study. The scoring system was by the over-all grading by counting the lesions.

If you looked at all the patients together, tetracycline, which we gave in a dose of 250 mg twice a day throughout the course, was superior to zinc. But if you came to compare the more severe type of patients

with those with the more moderate or milder acne, then zinc in the seven patients we had with severe acne did as well as the tetracycline group. So this perhaps may fit with some of the comments that Gerd Michaëlsson has made.

We have in England a zinc sulphate which is not the zinc sulphate complex. The zinc sulphate may be toxic and I would not recommend it, whereas the zinc sulphate-citrate complex, which you are using here is much safer. Out of 45 patients I have tried on the English zinc sulphate, one third have had to stop because of severe gastro-intestinal symptoms. We have had among our patients one who has perforated an asymptomatic gastric ulcer and there is another patient not far from Leeds, who also has perforated an ulcer on zinc sulphate, but I stress, that it is not the Draco zinc!

Plewig, Munich: Gerd Michaëlsson and your Scandinavian colleagues, if this is true what you have published and shown us today, especially in the severe ulcerating acne fulminans and in the inflammatory types, you should be congratulated, because it is an amazing finding and we wish that this is true. It would be a major break-through with a drug which evidently has very little side-effects. One question, do you see any side-effects in the skin? Dryness? Irritation?

Michaëlsson, Uppsala: Yes, we had some patients who claimed that their skin became dry and it seemed to be somewhat drier, but we did not do any quantitative measurements of sebum.

Plewig, Munich: Do you take the zinc before meals or after meals?

Juhlin, Uppsala: You should take it just after or with the meals. It is important that you do not take it before the meals.

van Vloten, Leiden: We have seen patients with severe zinc deficiency in long parenteral nutrition. They developed acne-like lesions during their illness. The histology showed an inflammatory infiltrate around the sebaceous follicle, like in acne, but no real comedo.

What stresses me most is that Drs. Baer and King can provoke in healthy individuals a zinc depletion. I thought it was very difficult to get zinc depletion in healthy individuals.

Michaëlsson, Uppsala: I think Baer and King had

these volunteers in the metabolic ward and they gave them only 0.2 mg zinc a day.

van Vloten, Leiden: But even then it is difficult to get the zinc depletion state.

Shuster, Newcastle-upon-Tyne: I think it is a general biological phenomenon that all new treatments are effective. But of course time often tells the story differently, and in assessing and in trying to predict what time will tell, one does have to say at the moment that it does not sound fantastically positive. But let us assume for the sake of argument that it is effective. Now, in astronomy for example, you cannot make a new observation unless you first have the theory which will confirm it. What is the theory here? Could we ask whether there is a change in sebum excretion? Could we ask whether the number of acne bacilli or sebum composition is altered, or whether — failing that — the injection of simple inflammatory agents in the skin produces a reduced reaction?

Juhlin, Uppsala: I think the last alternative you gave would be one of the best ways to prove the effect of zinc, because — at least to me — it looks like an effect on inflammation.

Shuster, Newcastle: Have you excluded a change in sebum excretion and in number of organisms?

Juhlin, Uppsala: We have made no measurements for the amount of bacteria or sebum. We have only shown that zinc has a better effect than placebo.

Cunliffe, Leeds: We have not looked at sebum excretion, but perhaps I could ask if you know of any effect of zinc on the various enzymes concerned with sebum synthesis? There have been two papers recently to show the zinc dependence of 5- α -reductase. As regards the bacteria we have looked at several zinc salts in vitro and it does nothing to either the *P. acnes* or the *S. epidermidis*. As regards the possible effects on mediators of inflammation, we have not worked on it, but there was one paper showing a dose-dependent effect on zinc reducing chemotaxis and one on zinc modifying the alternate complement pathway system.

Plewig, Munich: It is more a suggestion to Gerd Michaëlsson and van Vloten that just came to my mind. There was a peculiar disease described by

Schlappner et al (JAMA 1972; 219:877-80). Maybe you have seen this patient in Philadelphia? It was called "acute papulo-pustular acne associated with prolonged intravenous hyperalimentation". It was a patient who was unconscious; he was fed intravenously and he had an eruption of pustules in his face. Today it came to my mind that maybe the patient has had zinc depletion and an acneiform eruption?

Strauss, Iowa: The cutaneous hypo-alimentation syndrome is now seen quite commonly. The problem, however, is that these patients are not necessarily deficient only in zinc. Most of them are fed diets that are deficient in essential fatty acids etc.. So to label this as a zinc deficiency without more data is very difficult. We have looked at a few of these patients. They do have a characteristic pustular eruption on the face, but their zinc levels were normal.

I think that one of the problems in evaluating the use of zinc for acne is that there is no consistency in the type of zinc that is used. It seems to me that if there is an effort made to prove that these studies are true, somehow there has to be a standardization of the zinc product that is used. There are several studies that have been done in the United States with different zinc preparations. It seems to me there is time for some standardization at this point!

Michaëlsson, Uppsala: I would like to stress again that I do not think zinc has any effect on comedones and small papules.

Zachariae, Aarhus: I would like to ask you — have

you had any patients whom you have kept on tetracyclines and then added zinc? Does it work together synergistically?

Michaëlsson, Uppsala: Yes, we use them both sometimes. But it is important then that they are not given at the same time as zinc and tetracycline form a complex, just as iron and tetracycline do. Zinc orally and topical Vitamin-A-acid is also a good combination.

Schaefer, Berlin: If I remember right, zinc is a sort of binding ion between histamine and heparine in the mast cell? Could it be that mast cell depletion is somewhat reduced if you add zinc?

Strandberg, Uppsala: There is a large content of zinc in mast cells, that is true, but it has been amply shown that zinc has nothing to do with the binding between histamine and heparine whatsoever (Uvnäs et al, Acta Physiol Scand 1975; 93:401-08).

Juhlin, Uppsala: Dr. Michaëlsson, have you done any histological studies on the effect of zinc treatment?

Michaëlsson, Uppsala: No, I have not done any special studies, just some routine studies and there was nothing of significance.

Juhlin, Uppsala: It would be interesting if a good, extremely sensitive histological method could be found for identifying zinc in tissue.