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THE CLINICAL EFFECT OF CALCIUM OROTATE[1] ON CARTILAGE TISSUE

A Specific function in relation to pentose metabolism of bradytrophic tissue?

We are presenting here an orientation into the clinical effect of calcium orotate. Calcium orotate is absolutely free of any side effects and in this respect, it is far superior to all the conventional calcium salts now being used. Because calcium orotate can penetrate the complex cell membranes, it can compensate for a disturbed calcium transport through these cell membranes. In addition, calcium orotate has a special affinity for bradytrophic tissue—cartilage, for example—where it is metabolized. Parallel studies have shown that a defective calcium transport through the cell membrane is of great pathogenetical significance.

Previous experience, up to now:

We have employed calcium orotate extensively since 1968, hospitalized and ambulatory, to treat decalcification conditions and even in many cases, immunological diseases. The results accomplished here are in complete accord with what we discovered in 1959 concerning the transmembrane transport complex. Calcium is first released as an ion, on the cytoplasma membrane level, because orotic acid is chiefly metabolized there, not in the outer cell membrane. The clinical results that we have seen up to now are very encouraging, with a minimum of side effects completely unparalleled with anything that we have seen in the entire field of calcium supplementation.

And what is more, in suitable cases, this substance is a very satisfactory agent in the recalcification of metastatic defects in the skeletal system (1), (2). I reported this at the 1970 cancer congress in Houston.

The results of calcium orotate therapy with juvenile decalcification and with osteoporosis of the aged, are completely satisfactory for the first time, especially in view of the absence of side effects. This finding was contrary to all my previous experience with recalcification therapy.

The very remarkable results which we have achieved in hip joint plastic surgery, (3) are due to a hardening of the bone by preliminary treatment with calcium orotate. Previously, in this periodical, I reported the recalcification of bone metastases. Illustration 1. show another patient (f), in which a severe defect of the acetabular roof was so improved (recalcified), that hopeless

[1] also known as calcium diorotate

immobilization was replaced by fully normal, pain-free locomotive ability. This was accomplished after about 2.5g calcium orotate tgl[2] for 10 weeks. A long period of therapy with a conventinal calcium seltzer, had been carried out previously, with no effect.

Calcium orotate and Liver:
A several year search through many long term treatments with calcium orotate for side effects was absolutely negative. On the contrary, a whole series of positive observations came to light, which may be connected with the unique transmembrane calcium transport, we should mention here, that there is still quite a bit of clinical interest here. I will discuss this before I dwell on the main theme of the skeletal effect of calcium orotate.

One noteworthy observation is that patients with chronic cholangitis and light cases of chronic hepatitis—and also in severe aggressive cases—show a considerable improvement in their ailments, their state of health, their gall function, and to some extent, their biochemical and biological findings. This is especially true under long term therapy. It appears to be associated with an anti-inflammatory effect on the mesenchymal stroma system in the liver.

The carrier molecule—orotic acid—has an especially high affinity for mesenchymal tissue (4). Free orotic acid, magnesium orotate, or other calcium salts do not show this effect on the liver. We should refer here to the research of DEBORAH DONIACH (10) on all immulogical liver disease—with and without cirrhosis—concerning antimitochondrial (not anticellular) antibodies, as sickness motivation. Calcium orotate liberates its calcium ion—this is the classic anti-inflammatory principle—at the level of the mitochondrial membrane. This explains the anti-inflammatory effect in the liver.

Four patients who had taken, on the average, 3g of calcium orotate in stomach acid resistant capsules per day, for more than a year, submitted to a liver puncture. (For reasons which had nothing to do with the application of calcium orotate.) In all cases there was no sign of fatty liver development. Quite the contrary, three of the patients with stage 3 fatty liver showed a remarkable improvement under long term calcium orotate therapy.

The first patient was a teamster—very heavy consumption of alcohol. His condition had been a constant stage III for six years. After one year of therapy—tgl 2g calcium orotate—not only were the complaints lessened, but a liver biopsy showed nothing but a normal amount of fat accumulation.

Another patient—U.S. American (f)—came to us for treatment for a severe case of fatty liver. In just ten days, after tgl 6g calcium orotate therapy, the

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[2] tgl=daily (from the German "taglich")

complaint was improved and also a mild case of jaundice was cleared up, which had been with her for three years, following an influenza attack. After three weeks, a biopsy showed a dramatic improvement. Every possible liver therapy had been tried earlier, both in the United States, and here in Germany, with no success whatsoever. A third case of fatty liver III, showed a similar improvement after hyperalimentation.

It is absolutely necessary that we conduct a very thorough investigation on this effect of calcium orotate on fatty liver. We must remember that the lipase enzymes which are necessary for the mobilization of stored fat, are activated by Ca^{++}. I might assume, in this connection, that the primary source of fatty liver is a defective calcium transit in the liver cell. A magnesium washout caused by chronic alcoholism, in the liver cell membrane, could explain this. Mg^{++} is necessary in the cell membrane for Ca-transit into the cell. (6a) Anything which disturbs or injures the cell membrane function can affect calcium transit through the cell membrane. So there are possibly some other significant considerations, such as essential hypertonia or the ingestion of detergents which stick to kitchen utensils after washing. Also a fare too rich in carbohydrates puts a strain on the P-pools and likewise interrupts the Ca-transport through the membranes. Free orotic acid has no effect on the fatty liver condition. Likewise the same is true for magnesium orotate.

Effect on heart and circulation:
Another interesting observation is of a moderate, to often marked, dropping of the blood pressure with fixed hypertonia. This treatment will elevate the lowered blood pressure both in the chronic, as well as the light form of renal hypertonia. Normal blood pressure is not affected. What is especially convincing is the disappearance of angina pains, especially with a hypertrophied heart. In addition, the improvement is remarkably good with infarct anamnesis with hypertonia and a distinct sclerosis of the heart. Digitalis or Strophanthin tolerance appears to be better. With a dosage of 10g calcium orotate tgl., no incompatability of Digitalis can be observed, in the EKG, subjectively, or otherwise. Probably because no membraneous calcium ions are created. In this connection, I must point out that some time ago, KAUFMANN and coworkers (KAUFMANN and MITARBEIT) (11), researched the problem of defective or insufficient calcium transit in hypertrophia of the heart muscles. They conclude, that this is the reason for contractile insufficiency, in hypertrophy and other metabolic problems of the hypertrophic heart. Special reference must be made to the papers of the KAUFMANN group. We have made a series of tests with 14 year old dogs on a 14 percent incline. Our results were a very good confirmation of the pathogenetic mechanism that KAUFMANN portrayed. We will give you the details in a later article.

RILLING (12) has verified the research of ZONDEK (13) and KYLIN (14) with his comprehensive spectrographic studies. These authors maintain that essential

hypertonia is a cellular calcium-deficient pathognomonic condition. This interpretation is much the same as KAUFMANN'S explanation of heart muscle hypertrophy and would explain the blood pressure-lowering effect of calcium orotate. At the time that NIEPER and LABORIT were doing clinical research on potassium magnesium aspartate, we hoped to be able to correct disturbances of the heart action regulation system. Except for a suppression of ventricular and supraventricular extrastole, this hope was not realized. (15) As you know, the heart action regulation system is musculature in nature, which consists of a different type of metabolism, the direct oxygen or "pentose pathway". The stimulatory regulation and ganglion tissue provide especially good protection against oxygen deficiency intrafetally and later. Orotic acid plays an essential role in the pentose pathway, and so appears to be the electrolyte transporter needed for that tissue. In view of that, it should not be surprising to learn that we were able to normalize apparently therapy-resistant tachyarrhythmia with auricle flutter, in three cases, with a dosage of 5g calicum tgl.

After this excursus, I would like to mention the immune-inhibiting effect (as already reported) (4), of calcium orotate on a succession of bradytrophic tissues.

Specific effect on cartilage:
It was first reported by WHITE towards the end of 1969, that calcium orotate showed an astounding curative effect on the Tietze syndrome. These reports were repeated over and over during 1970 and 1971, so that we were induced to try calcium orotate in three cases of stubborn Tietze syndrome. The effect of the calium orotate was indeed surprising—all the details of the WHITE article were fully verified. Tietze syndrome, according to our information, is much more common in the US than here in Germany. According to WHITE, the syndrome is suppressed by very low doses—down to 1g/week, which we could verify. A dosage of 500mg/day is fully effective. It is highly significant that there is no effect whatsoever from calcium EAP, calcium-L dl aspartate (calciretard), calcium gluconate, calcium citrate, magnesium orotate, and K-Mg-aspartate, upon the Tietze syndrome.

On the basis of our knowledge of the effect of calcium orotate on the Tietze syndrome, we must conclude, that a favorable trophic effect on the cartilaginous intervertebral substance is the reason for the not infrequently spectacular improvement of the patient.

This fully specific effect of calcium orotate on cartilage, as evidenced by the Tietze syndrome experience, appears now to be of tremendous clinical significance. Unfortunately, we only learned this after the repeated reports of WHITE. While we were treating patients with spinal coumn syndrome and calcification damage, it had been apparent, for a long time, that the reported and verified improvement of their condition, must be attributed to more

than simply an influence on the bone tissue. For example, we had five patients (f) and one patient (m) from 26 to 76 years, with symptoms of weakness and painful sensitivity in the wrists. In three cases, it could be observed only with an sphygmomanometer, and in three cases observation was not possible at all. In every case, the complaints disappeared with calcium orotate therapy. Upon the removal of the therapy, or when the dosage was insufficient (less than about 1.6g/week) the complaints returned.

Especially puzzling are the findings for 18 patients from our files, in which there were severe dislocating alterations of the spinal column. Treated with calcium orotate, these patients became exceptionally free of complaints. Other medications—Butazonderivate, cortisone, indomethacin, physical therapy, gold medication—had failed. Even intensive treatment with calcium EAP, and calciretard along with calcim-sandoz and K-Mg-aspartate were ineffectual.

CASE HISTORY:

NOTE: *The illustration which are x-ray images are in German manuscript.*

Illustration 1, Frau K, 35 years old, before and after therapy with calcium orotate. Metast. Mamma-carcinoma

Illustration 2a, patient (f) H. Sch. 64 years
Severe complaint complex with LWS syndrome. Every imaginable therapeutic preventive measure taken to no avail. Infusion treatment with calcium-L-dl aspartate (calciretard) plus calcium EAP for more than six months. Complete stationary immobilization for three months 1970/71 to no avail. The pain associated with the LWS syndrome had forced her almost to the point of complete immobility. About three to five weeks after starting calcium orotate therapy—an average of 3g/daily—the patient was complaint free and remained so for 16 months—practically normal movement and walking ability. In contrast to calcium orotate, other calcium transporters such as calcium EAP and calciretard were fully ineffective. Is the improvement to be sought in a structurally favorable influence of the intervertebral tissue?

Illustration 2b,

Almost complaint free after six weeks intensive treatment with calcium orotate. Reconstruction mainly in the gap between 3 and 4. LWK Both developments are stabilized. These findings are not the only ones which gave rise to our questions about the effectiveness of calcium orotate on cartilage.

In 1968, we started using calcium orotate to treat patients with definite Bechterewschen disease. There were, in all, five such patients and in all the cases the very intense pain in the spinal column disappeared for the most part. All previous treatments—phenylbutazone, cortisone, gold therapy and healing baths—had been ineffective.

Illustration 3, patient (f) N. N. 56 years.

In 1963, the disease has progressed so far in this 56 year old patient, that she was almost completely immobilized. In spite of standard therapies and seltzer water cure, the progression continued. By 1968, the face was almost in a fixed position, movement and sitting were almost impossible. 1.5g calcium orotate was prescribed daily for 54 months continuously. No more complaints. The face could be moved normally and the patient resumed her household duties. The second picture is the patient (f) with Morbus Bechterew after 54 months continuous treatment with calcium orotate.

Illustration 4, patient (f) M.B. 71 years,

Most severe complaits for three years as a result of spondylitic arthrosis deformation. Treatment with phenylbutazone and also in combination with cortisone and with pyrazolone showed only slight palliative effect. Calcium-sandoz forte tgl. 3 tabl. for over four months without any effect. After 10 days tgl. 5g calcium orotate, the patient was almost complaint free, and has remained that way.

Illustration 5, patient (f) N.B. 81 years,

A sister of Frau M.B. above. 10 years older. Xrays and symptom complex indicate a very severe case. After being treated with calcium orotate tgl. 5g, she became complaint free, that she again took up vigorous employment after previous inactivity.

Illustration 6, patient R. 79 years (f)

Frau R., mentally and bodily vigorous. Had an acute attack of a long time existing osteochondrosis. Quite comfortable lying down, but experienced immediate unbearable pain in the spinal column upon standing up. After treatment with 5g calcium orotate daily, the patient became complaint free within three weeks. The pain had previously worsened under cortisone therapy. Calcium-gluconate-citrate, phenylbutazone and indomethazine had no effect whatsoever. The curative effect of calcium orotate was permanent (now over 14 months).

Illustration 7, patient (m) St. 55 years

Acute monarthritis of the right tibiotarsal joint, forcing him almost to the point of immobilization. Three tablets realin daily were of very little effect. Soludecortin H 50mg likewise. Volon 80 brought limited relief for 36 hours. Calcium orotate 8 tabl. each .5g daily brought improvement after 2 days and corrected the condition in 6. There are four similar cases.

Latest findings

By the end of 1972, we had experience with 21 cases of deforming spondylarthosis—five men, sixteen women, from 58 years up. Clinical and objective findings were consistent with the cases mentioned previously.

14 out of 16 women and 4 out of 5 men were helped by calcium orotate alone. They were observed for over a year. The remarkable effect of calcium orotate (called Ca orotate for short) with Tietze syndrome in the intervertebral disk (and possibly in the ligamentous apparatus) causes us to again evaluate the metabolic specificity of cartilage and other bradytrophic tissue. Here the pentose pathway (so-called direct oxidation) plays a very crucial role—an extremely old phylogenetic-metabolic pathway, which is not dependent upon the erythrocyte oxygen donation. In the pentose pathway, the ribose is activated through orotate coupling. For this reason, orotic acid plays a very essential role in the pentose pathway.

Here we are concerned with a large variety of tissues. Besides cartilage and ligamentous tissue, there is the connective tissue, the skin, the walls of the blood vessels, a specific section of the venules in the blood-brain-barrier, the heart stimulation-regulation tissue and keratin building tissue (hair, nails, etc.). Also the pentose pathway plays a very important role in the bone matrix, in the heart muscle and in the liver (both in the liver cells and in the stroma). The aromatic structure of the orotic acid is responsible for the high complex stability of the salts, and the already mentioned highly complex passage though the cell membrane typical of orotic acid, plainly make the orotate an ideal mineral transporter. (4)

We are indebted to the tireless effort of LABORIT (8) and his scholars (7) who made public the results of their year-long research program which disclosed the vital effect of the pentose pathway in the function and structure of bradytrophic tissue. Life would not be possible without it. Previously, cartilage and connective tissue had been considered uninfluencable, for the most part.

If calcium orotate can bring about a change here, as was demonstrated, then there is not much value in the geriatric therapeutic concept.

Summary
An orientation is given concerning the clinical effects of calcium orotate (called Ca orotate for short). Because calcium orotate is free from side effects,

it is superior to conventional calcium salts, which have certain problems when applied in osteoporosis with concomitant arteriosclerosis of the abdominal aorta. Calcium orotate, on the other hand, protects the body from arteriosclerosis.

Calcium, for this reason, is of value as a food supplement when used in the form of calcium orotate, which can penetrate the cell membranes as a complex form, compensating for defective calcium transit into the cells. In addition, calcium orotate has a special affinity for cartilage and other bradytrophic tissue, where it is metabolized.

Not only is the basic principle of action quite simple, but the long time therapeutic effects are of considerable interest. A new dimension of therapy now appears with the improvements in osteochondrosis and disk degeneration treatment. Far better than the present therapeutic possibilities. Much the same observations seem to apply to osteoporosis.

Parallel investigations point to the important pathogenetic significance of a defective calcium transport through the cell membrane. This is the case, for example, in hypertensions—especially essential hypertension—in fatty liver, in disturbances of the ductile of the heart, and in contractile and metabolic insufficiency of the hypertrophic myocardium. In respect to all of these indications, calcium seems to bring about the most promising therapeutic results, when combined with the carrier orotic acid for better transmembrane transport, in the form of calcium orotate.

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