COMMENTS BY HANS A. NIEPER, MD. ON THE ARTICLE PUBLISHED BY THE HACHEN MS KLINIK

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After just a short time of clinical application, some of the MS-related disturbances, especially those cerebellum-related such as vertigo and ataxia, show considerable improvement. Proof of this was first reported in an article published by a German MS clinic in Hachen back in 1968. On the basis of this research report, the German Ministry of Health (the German equivalent of the American FDA) which had (already) officially declared Calcium EAP to be an MS medication (as well as several other indication declarations) two years earlier now revised that declaration to "for cerebral ataxic forms of MS". (See the information slip that accompanies the product.) Strictly speaking, this revised declaration is incorrect. According to long term observations we have discovered that other MS symptoms can have better improvement than the ones related to the cerebellum. (We should, however, mention that another phase of cerebellum -related sickness, the so-called familial "Cerebella-Atrophy", is not influenced by the EAP salts.) I have never applied for a correction of this indication declaration since multiple sclerosis is still listed as an indication on the packages of calcium EAP. In fact, the available results from a long-term study, over 20 years, of this therapy, are really remarkable.

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Calcium Carrier Substances in the Treatment of Cerebellar Atactic Forms of Multiple Sclerosis

From the Sauerlandklinik Hachen, clinic for patients with multiple sclerosis and metabolic diseases

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Studies aimed at testing the possibility of treating certain forms of multiple sclerosis with calcium carrier compounds have been performed at the Sauerlandklinik, West Germany since early 1966. Calcium aspartate (Calciretard^{R}) and calcium-2-aminoethanol phosphate (Calcium-EAP^{R}), both manufactured by Dr. Köhler-Chemie, D-6146 Alsbach-Bergstrasse, West Germany) were suitable calcium carriers.

Based on previous experiments and experience gained to date with the electrolyte carriers magnesium aspartate and potassium aspartate, it was only natural to consider the selective transport of calcium into the cell by calcium aspartate and Calcium-EAP as possible therapeutic modalities. The objective of the study, then, was to investigate whether calcium carriers showed advanced antiallergic and antiinflammatory activity.

Calciretard^{R}, i.e., calcium aspartate, could be shown in dermatology patients to be markedly more active against eczemas than calcium gluconate. Therapeutic success could be achieved with Calciretard even in patients with therapy-resistant mucous colitis and ulcerative colitis. It was therefore assumed that the selective transport of calcium in the form of aspartate into the cell or cell membranes may be responsible for the highly effective antiinflammatory action of Calciretard. Unlike Calciretard, Calcium-EAP^{R} is thought to act on other targets as a result of its specific affinity for the epidermis, inflamed or regenerating organs, tumors, lymphocytes, as well the liver and muscles. Since it forms relatively few dissociating salts and is broken down by cell metabolism, Calcium-EAP is considered a particularly suitable calcium carrier. Its prime site of action appears to be the cell membrane. It has been suggested that the carrier compound Calcium-EAP alters the saponification pattern of the lipid bilayer of the cell membrane after being selectively transported into the cell membrane and

subsequently releasing calcium at the target site. Whereas the lipid bilayer is permeable upon saponification with potassium, sodium and magnesium, it is not following saponification brought on by calcium: Here, the access of all aggressive substances to the cell is inhibited or even blocked completely; however, the egress of antibodies produced in the cell is equally impaired.

In this context, I would like to cite more recent works by Ross, who saw a precipitation phenomenon in the serum of multiple sclerosis patients when adding extracts of normal human brain tissue. He accounted for this phenomenon by an antigen-antibody reaction that is triggered by a chemically definable factor showing particular characteristics, which is typically demonstrable in the serum of MS patients suffering acute episodes of the disease. According to Ross, the occurrence of such a factor and the precipitation phenomenon are strong evidence of the assumption that autoimmunization processes take place in the course of multiple sclerosis. This theory is supported by observations made in fluorescence microscopy studies at the Göttingen Pediatric University Clinic in patients with van Bogaert's sclerosing leukoencephalitis, a disease which no doubt is related to multiple sclerosis.

When starting clinical trials with Calcium-EAP, Nieper found that this substance, especially following i.v. injection, gave rise to shivering, chills and transient headache in patients with latent or manifest hepatitis or large tumors. It was assumed that, in these two indications, ethanolamine was released from Calcium-EAP at an exceptionally high rate. Occasionally occurring fever reactions in patients on long-term Calcium-EAP therapy may be prevented by coadministering Trophicard^{R} (potassium DL-aspartate, magnesium DL-aspartate).

In experiments on rats it was, among other things, found that EAP (= phosphoryl colamine) may have anabolic effects. The weekly recordings of the weights of the rats showed weight gains for the female animals, whereas the male rats were found to have put on much less weight. Also, during the six months of the experiments, the female animals were balanced, peaceful and even-tempered, and their coat clean and smooth, whereas all male rats were exceptionally aggressive and prone to biting, and had dirty, shaggy coats.

The test animals were given 300 mg Calcium-EAP per kg body weight per day. The daily therapeutic dose in man is usually 5.7 to 11.4 mg/kg i.v. or 20 to 40 mg/kg by the oral route.

Histological examination of liver, heart muscle, kidney, spleen, stomach, and lung tissue of animals treated with Calcium-EAP revealed no indication of any pathological parenchymal changes that might suggest chronic toxicity. One of the ten test animals was found to have renal calculi.

In the clinical trial phase, patients on Calcium-EAP were monitored with respect to blood counts, ESR, clotting time and cholinesterase. No major changes that might be attributable to the intravenous administration of calcium could be detected.

Observations by the author: Among the approximately 900 multiple sclerosis patients admitted to the Sauerlandklinik between February 1, 1966 and January 31, 1967, 167 individuals presented with a predominantly cerebellar-atactic syndrome. This group comprised patients with relatively mild cerebellar symptoms as well as persons with most severe manifestations of the disease, which had left the patients utterly helpless. --- It is

well known that exactly these cerebellar-atactic syndromes and courses of multiple sclerosis are extremely resistant to therapy or cannot be treated at all. --- We assigned our patients to 3 groups: Group 1: mild cases; Group 2: moderately severe cases; Group 3: severe cases. --- The mild cases showed weak intention tremor and mild ataxia in the upper and lower extremities with slightly atactic gait, but the patient was still able to walk unaided. --- Moderately severe cases presented more severe ataxia and a correspondingly more pronounced intention tremor in the upper extremities; these patients barely managed to point their noses; speech was clearly staccato; gait moderately atactic, forcing the patient to use a stick for walking. --- The severe cases presented heavy tremor of the head, extremely pronounced ataxia in the upper and lower extremities with heavy intention tremor so that these patients were no longer able to point their noses; speech was heavily syllabized and more or less unintelligible; tremor increased with any voluntary movement and when the patient spoke; gait in those patients who were barely able to walk was so severely atactic that these patients depended on the use of a stick and a walking aid.

Treatment of the patients mentioned above was instituted by giving i.v. Calcium-EAP injections of 10.0 of a 4 % solution three times per week or 5.0 daily. To prevent the adverse reactions discussed above, 1 tablet Trophicard (125 mg potassium aspartate and 125 mg magnesium aspartate) three times daily was coadministered. Commensurate with the severity of the individual case and condition of the patient, the usual MS treatment was given. ---

Improvement in the cerebellar-atactic symptoms as a result of Calcium-EAP therapy meant: (1) complete disappearance of symptoms in mild cases; (2) mild atactic symptoms in moderately severe cases; (3) improvement in

the cerebellar-atactic symptoms to such an extent that only mild intention tremor and mild ataxia in the upper and lower extremities remained, the patient was able to eat by himself and to walk with a stick yet without requiring an additional walking aid.

Sixty-three of the 167 patients participating in this study were assigned to Group 1. Improvement was good in 29, or 46 %, of these cases; 27 % each showed slight improvement or remained unchanged. In other words, of our 63 mild cases, we discharged 17 patients with a slight improvement in their symptoms, and another 17 without any improvement.

Sixty-six of the 167 patients belonged to Group 2. Of these, 22, or 33 %, had clearly improved when discharged. Twenty-five patients, or 38 %, showed a slight improvement, whereas the other 19 patients, or 29 %, were unchanged.

The remaining 38 patients had been assigned to Group 3, i.e., the group of severely ill patients. Here, only 6 individuals, or 16 %, showed clear improvement in their symptoms. In 15 cases, or 39 %, a slight improvement could be achieved, whereas in the other 17 cases, or 45 %, no improvement was seen.

To sum up, in our mild cases we saw clear improvement in 46 % of our patients; in our moderately severe cases, in 33 %; and in our severely ill patients, in merely 16 %. This result thus clearly shows that the probability of therapeutic success rapidly dwindles as the severity of cerebellar-atactic symptoms increases.

Of our 167 mild, moderately severe and severe cases, 57, or 32 %, had markedly improved when discharged. Thirty-two of the 57 patients were women, roughly reflecting the male-female ratio of the total number of patients

admitted. Of these 57 successfully treated patients, only five (3 women and 2 men) were over 50 years of age. Individuals between 25 and 45 responded best to therapy with Calcium-EAP.

The side effects of Calcium-EAP observed in the animal experiments, such as the anabolic effect in female rats and the markedly increased aggressiveness of the male animals was not seen in our patients. Nor were adverse reactions such as anginal complaints, biliary dyskinesia, shivering, chills and fever observed in our patients, probably as a result of the concurrent prophylactic administration of Trophicard^{R}.

In light of these results, treatment of cerebellar-atactic symptoms in multiple sclerosis patients with Calcium-EAP may even be given in higher doses than those used by us.

Before employing Calcium-EAP in patients with cerebellar-atactic forms of multiple sclerosis we checked whether the improvements obtained by Calcium-EAP therapy were not, in effect, due to spontaneous remission. To do this, we reviewed a control group comprising a total of 61 patients treated in 1965, who were also classified according to severity, but who had not been given specific therapy for cerebellar-atactic symptoms.

According to the severity of the patients' condition, 40 patients were assigned to Group 1 (mild cerebellar-atactic symptoms); 16, to Group 2 (moderately severe cases); and 5, to Group 3 (pronounced degenerative changes).

A slight subjective improvement had been reported in only 6 patients of Group 1, and in 3 patients of Group 2. A somewhat more pronounced improvement in the cerebellar-atactic symptoms had been found in 2 patients

of Group 1, and in one case of Group 2. Although the usual treatment had been given, the cerebellar-atactic symptoms had even exacerbated in 2 in-patients of Group 3. No changes had been seen in 47 of the 61 control patients.

Spontaneous remission with respect to the cerebellar-atactic symptoms could be excluded in all 61 of these patients, both during therapy and in their entire histories.

Calculation of the percentages for the control patients shows that these are negligible compared with the results of Calcium-EAP therapy, especially since the few improvements in Groups 1 and 2 were only subjective ones, which were not accompanied by a lessening of the neurological symptoms.

We are at a loss for an explanation of our observation that Calcium-EAP apparently improves the cerebellar-atactic symptoms to the extent reported in this paper. Calcium-EAP failed to improve other syndromes of multiple sclerosis. It can therefore be said that Calcium-EAP apparently offers a therapeutical approach that achieves a more or less pronounced alleviation of cerebellar-atactic symptoms, which had hitherto been particularly difficult to treat.

Summary

Calcium carrier compounds in the form of calcium aspartate and calcium-2-aminoethanol phosphate may influence the saponification pattern and permeability of the lipid bilayer of the cell membrane by the action of calcium that is specifically introduced into the cell and released in ionized form at the target site so that the

access of all aggressive substances to the cell is inhibited or even blocked. On the other hand, this process also means that the egress of antibodies from the cell would be impaired. --- For the reasons discussed, the use of calcium carrier compounds is considered especially suitable in antiimmune and autoimmune diseases. --- Since current medical opinion discusses such an autoimmune response genesis also for multiple sclerosis, we administered calcium-2-aminoethanol phosphate (Calcium-EAP) to MS patients at our clinic. Since only the cerebellar-atactic symptoms of multiple sclerosis could more or less be influenced by Calcium-EAP therapy and no effects could be observed in all other forms of multiple sclerosis, we performed statistical analysis of the results of 167 patients with cerebellar-atactic symptoms. We assigned our patients to three groups according to severity. --- Group 1 (mild cases) comprised 63 patients, 29 of whom, or 46 %, showed a marked improvement. Group 2 (moderately severe cases) comprised 66 patients, 22 of whom, or 33 %, showed clear improvement when discharged. The remaining 38 patients were assigned to Group 3 (severe cases). Here, only 6 patients, or 16 %, showed a marked improvement. --- This result thus clearly shows that the probability of therapeutic success rapidly dwindles as the severity of cerebellar-atactic symptoms increases. Of our 167 mild, moderately severe and severe cases, 57, or 32 %, had markedly improved when discharged. Individuals between 25 and 45 responded best to therapy with Calcium-EAP. No adverse reactions were seen during treatment with Calcium-EAP and Trophicard protection. A control group of 61 patients who had not been given Calcium-EAP therapy failed to show comparable results.

References

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