CHELATION THERAPY FOR THE TREATMENT OF ATHEROSCLEROSIS: AN APPRAISAL

Prepared by the Ad Hoc Committee on Chelation Therapy,

Hennepin County Medical Society

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Brief Summary of Chelation Therapy for the Lay Public

Chelation therapy refers to the use of sodium EDTA* to treat certain types of atherosclerosis (hardening of the arteries) such as angina pectoris, intermittent claudication of the leg, or cerebral vascular disease. EDTA is generally administered intravenously over a period of three to four hours several times weekly for a total of 20 to 40 treatments. The course of treatments is sometimes repeated after a rest period. Vitamins, minerals, and other drugs are often administered at the same time. The cost of a course of therapy is typically $1,500 to $3,000.

The Hennepin County Medical Society has reviewed the use of chelation therapy and concluded that:

1) There is no objective evidence that chelation therapy is effective in treating any form of atherosclerosis or heart disease.

2) Excessive doses of EDTA can cause numerous side effects, including damage to the kidneys. The long-term side effects of EDTA have not been adequately studied

3) Because EDTA has not been shown to be an effective therapy for atherosclerosis and there is concern about its safety, chelation therapy should should not be used for this purpose. It is inappropriate and misleading for medical practitioners to offer chelation therapy to patients as an "experimental" therapy if it is being administered as a routine clinical therapy rather than as part of a scientific study.

*Sodium ethylenediaminetetraacetic acid.

Further information is available upon request from the Hennepin County Medical Society.

Background

Ethylenediaminetetraacetic acid (EDTA) is used in industrial applications and in the laboratory because of its ability to bind (chelate) divalent and trivalent metals. The sodium salt of this compound (Na_2EDTA) with which this report is concerned binds calcium avidly and, when administered to animals or humans, can cause hypocalcemia. Because of this property, Na_2EDTA has been used to treat hypercalcemia. The only current FDA approved uses of Na_2EDTA are for the treatment of hypercalcemia or digitalis toxicity. The calcium salt of EDTA (CaEDTA) can bind metals with a higher affinity than calcium for EDTA (lead, mercury, zinc) and is used clinically to treat heavy metal poisoning. CaEDTA is less toxic than Na_2EDTA because it does not produce hypocalcemia.

The clinical use of Na_2EDTA to treat diseases associated with calcium accumulation in tissues was first suggested in 1955 when repeated doses were anecdotally reported to successfully treat nephrocalcinosis.[1] The authors of this report suggested that Na_2EDTA might also be of benefit in removing the calcium which is a component of atheromatous plaques. A number of authors in the late 1950's and early 1960's reported their favorable experience with the use of Na_2EDTA to treat various manifestations of atherosclerosis. After this initial enthusiasm, however, interest in chelation therapy waned and few additional reports appeared in the medical literature. Prevailing medical opinion in the 1960's and 1970's was that chelation therapy had not been shown to be an effective treatment for atherosclerosis.[2,3] The suggested rationale for using Na_2EDTA, removal of calcium from atheromas, has been questioned since calcium is only a minor component of these lesions.[4] A variety of alternative mechanisms have been offered, including effects on unspecified enzymes due to binding of heavy metals, changes in blood coagulation, and inhibition of vasospasm.

Over the past five years, chelation therapy has enjoyed renewed popularity among a small number of physicians. Courses of chelation therapy for the treatment of atherosclerosis are currently offered by physicians in many parts of the United States, including Minnesota.[5] Na_2EDTA is generally administered intravenously at a dose of 0.5 to 3 grams in one liter of fluid over a period of three to four hours. A typical course consists of one to three treatments per week for a total of 20 to 40 treatments, although the number and frequency of treatments varies. After several weeks rest, the course is sometimes repeated and some patients receive more than 100 treatments. A variety of drugs (lidocaine, heparin), vitamins and minerals may be added to the intravenous infusion. Oral vitamin and mineral supplementation is common, as is the concurrent use of a low fat, low cholesterol diet.[6,7]

Efficacy of Chelation Therapy

Available reports of chelation therapy describe the administration of Na_2EDTA to patients with various forms of atherosclerosis, principally angina pectoris. Each of these reports compares patients before and after receiving Na_2EDTA, and none of the studies uses a control group. The following are the larger and most completely described series of patients.

Clark et al. (1956) reported 20 patients with angina pectoris treated with Na_2EDTA at a dose of 5 grams per treatment administered 5 days per week for a mean of 35 treatments (range 15 to 60 treatments).[8] Criteria for angina pectoris are not explicitly described. Nineteen of 20 patients reported subjective improvement in symptoms. Improvement in exercise tolerance is also reported, but the method of testing exercise tolerance is not described. In 6 patients, abnormal electrocardiograms were reported to revert to normal during or following therapy. One patient in this series died suddenly, and the authors speculate that this could have been due to a calcium embolus to the brain.

The same author, in a 1960 editorial, describes his experience with "several hundred patients" stating that symptomatic relief was obtained in 80% of patients with angina pectoris.[9] He also mentions that the best results in his experience are obtained in patients with intermittent claudication. No data are presented regarding either type of patient.

Meltzer et al. (1960) reported 10 patients with angina given three to four grams of Na_2EDTA two to four times weekly for a total of 20 treatments.[10] No improvement was noted at the end of the treatments, but two to three months later nine patients noted improvement in symptoms and decreasing use of nitroglycerine. Five of nine patients were felt to have a more normal electrocardiogram, and three patients had a decrease in heart size on chest x-ray.

In 1963, Kitchell et al. reappraised the 10 patients described above, (Meltzer et al.[10]) and reported the treatment of an additional 28 patients with angina pectoris.[11] Patients again received three to four grams Na_2EDTA two to four times weekly. The total number of treatments ranged from 20 to 95, and the duration of follow up was 1.5 to 4 years. Of the original 10 patients evaluated five years after initial therapy, 5 had died of myocardial infarction, 3 had no change in symptoms, and only 2 were improved. Of the 28 additional patients in this study, 66% were reported to have increased exercise tolerance three months after the end of their treatments. After 18 months, however, 7 had died of myocardial infarction, 2 were worse, 6 were unchanged, and 13 were improved. The authors of this study felt that chelation offered no benefit over traditional therapies. It should be noted that these authors attempted a placebo controlled crossover study but were unable to complete this because of the large number of patients dropping out of the study.

More recently, patients with coronary artery disease[19] were studied before and after 20 weekly infusions of Na_2EDTA. Mean left ventricular ejection fraction

measure by radionuclide scintigraphy increased after treatment, but the magnitude of this increase (5.8%) was small. No untreated subjects were studied over a similar time period to serve as a control group.

Some studies report a decrease in serum cholesterol after Na_2EDTA therapy.[6] However, subjects in these studies were also placed on a low fat, low cholesterol diet which could account for this observation.

In summary, several reports describe improvement in symptoms due to atherosclerosis following chelation therapy. The study with the longest period of follow up, however, reports no benefit from chelation. All of these reports suffer from flaws in experimental design, such as inadequate description of patient characteristics, inadequate description of methods used to assess improvement, and a lack of control groups. As a result, it is difficult to draw any conclusion regarding the efficacy of chelation therapy as described in these studies.

Animal Studies

Koen, et al. administered Na_2EDTA or placebo to rats fed an atherogenic diet and found less aortic atherosclerosis in the EDTA treated animals.[12] The dose of Na_2EDTA, however, was 400 mg/kg, 10 times more on a weight basis than is used in humans. Na_2EDTA has also been shown to remove calcium from vascular plaque of blood vessels perfused in vitro with very high concentrations of the drug (5 grams/100 ml.).[13] The relevance of these observations to the clinical use of Na_2EDTA is unclear.

Toxicity

Fatal and nonfatal renal injury have been reported in patients receiving Na_2EDTA. Renal insufficiency may be accompanied by urinary frequency and urgency, or by other systemic signs of toxicity as discussed below.[14] The urinary sediment may contain red blood cells, white blood cells, epithelial cells and granular or cellular casts. In fatal cases, histologic changes typical of acute

tubular necrosis are observed.[15,16] Although renal injury appears to be dose related and most common in patients receiving greater than 5 grams daily, several fatal cases received only 2 to 3 grams daily.[16,17] Renal injury with a similar histologic appearance has been demonstrated in rats receiving Na_2EDTA.[15] This injury did not occur at doses of less than 62.5 mg/kg, and it has been suggested on the basis of this study that doses of less than 62.5 mg/kg are also safe in humans. Because of species differences, this assumption may not be valid.

Other toxic effects reported with the administration of Na_2EDTA include hypocalcemia, loss of digitalis effect, increase in prothrombin time, decreased insulin requirement in diabetics, hypotension, burning at the infusion site, nausea and vomiting, and a histamine-like reaction with sneezing and pruritis.[18,19] A rash has been reported similar to that seen with pyridoxine or zinc deficiency; supplementation with these two factors to prevent the rash is common. All of these acute side effects of chelation therapy appear to be dose related dand uncommon at the doses currently used. Since Na_2EDTA is eliminated almost entirely by renal excretion, its use is not recommended in patients with renal insufficiency.[5]

Chronic toxicity from Na_2EDTA has not been extensively evaluated. Monitoring of renal function during prolonged therapy is not well documented, and consequences of calcium mobilization such as changes in bone mineralization and parathyroid function have not been studied. Ingestion of Na_2EDTA by female rats during pregnancy causes congenital malformations in offspring which can be prevented by simultaneous administration of zinc.[20]

Cost of Therapy

The cost of a course of chelation therapy with Na_2EDTA is reported by the American Academy of Medical Preventics to cost $2,000 to $3,000.[4] One practitioner offering this therapy in Minneapolis charges approximately $1,800 for a course of 30 treatments.

Conclusions

The use of Na_2EDTA to treat atherosclerosis is not supported by the available data. All studies claiming therapeutic benefit are flawed in one or more aspects of experimental design, the most important of which is the lack of suitable control groups. The clinical use of Na_2EDTA to treat any form of atherosclerosis has no scientific basis and is not an acceptable therapy for this disease.

Acute toxicity from Na_2EDTA can generally be avoided by limiting the dose to less than 3 grams daily, but adverse effects including renal injury have been reported even at lower doses. The long-term safety of chelation therapy has not been adequately evaluated.

EDTA chelation therapy should be regarded as investigational because of a lack of objective evidence of its efficacy and questions regarding its safety. Studies involving the use of Na_2EDTA should be performed by trained investigators using rigorously designed protocols capable of providing useful information. It is inappropriate and misleading for medical practitioners to offer chelation to patients as an "experimental" therapy if the drug is being administered as a routine clinical treatment rather than as part of such a study.

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Appendix 1

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