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Value of EDTA in atherosclerosis

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The problem of atherosclerosis and its sequelae, mainly in the form of cerebrovascular or cardiovascular morbidity and mortality, is by far the largest health problem affecting the Western world. Attitudes to its preventability and reversibility have ranged from the extremes of those who feel it is completely preventable and substantially reversible to those who regard it as an inevitable ageing process for which there is no remedy. It is clear that dietary and life style habits play an important role in the earlier onset of atherosclerosis, and observation of different populations in developed and developing countries has stimulated the present interest in preventive means, especially in relation to diet. There are many other factors that can predispose the individual to atherosclerosis, of which the most important can be listed as male sex, age, hypertension, diabetes, smoking, a family history of premature arterial disease, certain rare metabolic defects, for example, homocystinuria, and — though this is more controversial — lack of exercise and mental stress. Thus, any approach to the population in general or the individual patient must be multifactorial. If medical problems are excluded, the life style factors that are generally accepted as preventing premature atherosclerosis are: changes to the diet, emphasizing a lower fat intake in favour of predominantly unsaturated fats; stopping smoking (very important); and the encouragement of exercise, although the last is still not proven.

Regression of atherosclerotic lesions

Drug therapy aimed at inhibiting or causing regression of atherosclerosis is still in its infancy. A great deal of animal experimental work has revealed a number of agents that are capable of suppressing atherosclerosis. These drugs have included the calcium antagonist Lanthanum (Kramsch et al., 1980), EDTA (Wartman et al., 1967), pyridinol carbonate (Kramsch and Chan, 1978) and Chondroitin sulphate A (Morrison et al., 1972), Reserpine, Guanethidine and Propranolol (Whittington-Coleman et al , 1970, 1973), Calcitonin (Chan and Kramsch, 1978), Sodium p-Hexadecyclaminobezoate (Katocs et al., 1977, Hollander et al., 1978), Manganese, Oestrogen and certain phosphodiasterase inhibitors (Numano et al., 1976, 1978), Ethane-hydroxydiphosphonate (Hollander et al., 1979), Colchicine, and Penicall amine (Hollander et al., 1979). None of these drugs appear to have gained general acceptance in the clinical setting for this purpose. Indeed, the evidence for regression of atherosclerotic lesions in man is extremely limited, although recent work using the technique of plasmapheresis of LDL cholesterol is encouraging. The need for large, expensive, and lengthy studies to alter the natural history of atherosclerosis, using as the end point either clinical episodes or death, has been a considerable deterrent. The only alternative so far has been the repeated use of arteriography, but this should be restricted to very few patients. New techniques of ultrasound colour imaging of atherosclerotic plaque lesions or the use of monoclonal isotope-linked antibodies to these lesions may enable us to examine patients in greater numbers sequentially.

Therapy with EDTA

For many years physicians in the United States and in European countries have used the chelating agent EDTA as an anti-atherosclerosis drug. A very large anecdotal history has grown up supporting its value (Walker, 1982). In the 1950s and 1960s a number of uncontrolled trials reported favourably on its value in cerebrovascular disease, ischaemic heart disease, and peripheral vascular disease. However, none of these trials was properly controlled by the double blind procedure, and thus the use of EDTA has not gained acceptance among the majority of physicians. Currently a large double blind trial is proceeding in the United States, with the approval of the FDA, under the auspices of the International Chelation Research Foundation (Rubin, 1986). The present objective of this study is to determine whether infusions of 3g of EDTA in 500cc of normal saline infused intravenously over three to four hours, three times weekly over 10 weeks, has a significant effect on patients suffering from intermittent claudication due to peripheral vascular disease. Treadmill testing will be the principal method of evaluation. Over the past three years we have been examining the effects of EDTA administered in the above manner in patients with evidence of atherosclerotic vascular disease. This has been in a purely clinical private setting, and so the approach has been multifactorial, with particular emphasis on low cholesterol dieting, exercise, and reduction of stress. The addition of EDTA infusions to this approach has meant that we have not been able to study it independently of these other variables.

However, certain findings are, I believe, noteworthy. During infusions, hypertension is particularly well controlled, probably through an action on calcium in the peripheral vascular system; but this does not eliminate the need for oral anti-hypertensive treatment after infusions have been completed. Although present dogma insists that anti-hypertensive treatment is lifelong, it is possible that a sub-group of patients who are well-controlled over several months may become permanently normotensive. There is some indication that this may occur after EDTA infusions, and it will require further study.

Initial reactions of symptom improvement occur in 80 per cent of patients (unpublished observations), but when patients were questioned from three to 12 months after completing treatment with a retrospective questionnaire there was a 65 per cent response, and of the responders approximately 70 per cent felt that their improvement had been maintained. Unfortunately the poor response to the questionnaire makes it difficult to interpret these findings.

Interesting side benefits from the treatment — which were reported by a large majority of patients — included improvement in vision, skin tone and colour, tinnitus relief, and general alertness, concentration, and memory.

In patients with peripheral vascular disease, initial treadmill studies showed that most patients had improved by at least 50 per cent, judged by walking times on the treadmill. In a further pilot

group of patients studied by stress ECG, while patients felt that their angina had improved, on repeat stress testing similar ST depression changes were seen at approximately similar times during the Bruce protocol. Thus, patients may claim considerable clinical improvement without this being borne out by present methods of testing.

Using real time Doppler techniques, we have seen improvements in wave patterns in the carotid and lower limb vessels (unpublished observations), and in some patients we have had the opportunity of studying middle cerebral blood flow, but as yet no striking changes have occurred. Using Technetium as the isotope, some striking improvements in brain blood flow in both hemispheres were reported (Casdorph, 1981), and it would be extremely encouraging if these studies were confirmed in a more detailed and exhaustive manner. It is possible that confusion has arisen where changes may have occurred in the microvascular circulation, which such isotope studies would show (unlike Doppler studies of the middle cerebral artery). In addition, an effect on the microcirculation of the arterial wall might lead to changes in real time Doppler findings. It remains to be seen whether duplex Doppler imaging, or further colour imaging of atheromatous plaques and blood flow across them, will be able to show regression in lesions. No arteriographic changes have yet been published to determine whether changes have taken place. This would, of course, only be of value in the main arterial vessels.

Possible mechanisms of action of EDTA in atherosclerosis

We know from animal experiments that EDTA is an effective anti-atherosclerotic agent (Wartman et al., 1967). However, the dose levels used were much higher than could be tolerated in human subjects. At a dosage of 3g a mild hypocalcaemic effect is seen, and it is this effect on calcium at the extracellular and intracellular level that may explain its anti-atherogenic action in animals.

The importance of calcium in its role as second intracellular messenger, in enzyme activity, blood clotting mechanisms, muscular contraction and relaxation, nerve conduction, and many other functions has made it central to a wide variety of physiological processes. It remains to be seen which of these might be of importance in the anti-atherogenic action. The prevention of platelet thrombosis is one possibility. A direct attack on the atheromatous lesion by removal of calcium or by a secondary stimulation of parathyroid hormone action on the arterial wall has been another hypothesis. The latter would be expected to have an effect on arterial compliance or elasticity, and as aortic compliance can be measured simply (Gosling and King, 1978), we have been examining this possibility.

Rapid relief of symptoms may occur in a manner similar to that of the calcium antagonists verapamil and nifedepine. These prevent calcium entry into the cell, thus preventing calcium overload in the ischaemic tissue. It appears that a cell that is ischaemic may be damaged not so much by the lack of oxygen or other nutrients supplied as by an effect of calcium accumulation in the cell, which in turn damages other enzyme activities, in particular oxidative phosphorylation. It has been shown that EDTA is effective in preventing this and overcoming the inhibition of oxidative phosphorylation in the ischaemic cell (Peng et al., 1977). This may explain the rapid movement in symptoms in some patients early on in treatment. Those who have used EDTA have been impressed by the dramatic effects that can occur in some patients, and this action might also be explained by its powerful antidepressive effect, shown in a double blind trial over and above any placebo action (Kay et al., 1984).

Clinical use of EDTA

This should only be done in an experienced centre where a careful evaluation of the patient's vascular status is possible. Real time Doppler monitoring of carotid and peripheral circulation with the added facility of duplex imaging and measurement of arterial compliance is advisable. Careful monitoring of renal function is essential. In the past, when much larger doses were given by rapid infusion, nephrotoxicity was seen. However, infusions taken over three and a half to four hours are extremely safe. For patient management a careful evaluation of all the factors contributing to arterial disease is essential. These can then be modified as far as possible, and in particular the importance of lowering the total cholesterol to levels below 5mmol per litre might result in long-term regression of lesions.

The future

Prevention of atherosclerosis will be the cornerstone of future efforts, with sub-groups of patients identified with genetic predisposition or metabolic errors. In the meantime it will remain important to explore existing and new drugs that have an anti-atherosclerotic action. It would be an achievement if the atherosclerotic plaque lesion was stabilized by such drugs and future thrombosis on the lesion prevented. Use of EDTA in this setting will remain limited to special centres until the encouraging clinical evidence is supported by the current double blind trials in progress, or until evidence of definitive arterial or ischaemic cell improvements are identified technically or biochemically in individually studied patients. A much bigger effort than has been supported/funded in the past will be necessary to achieve progress in this field. □

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